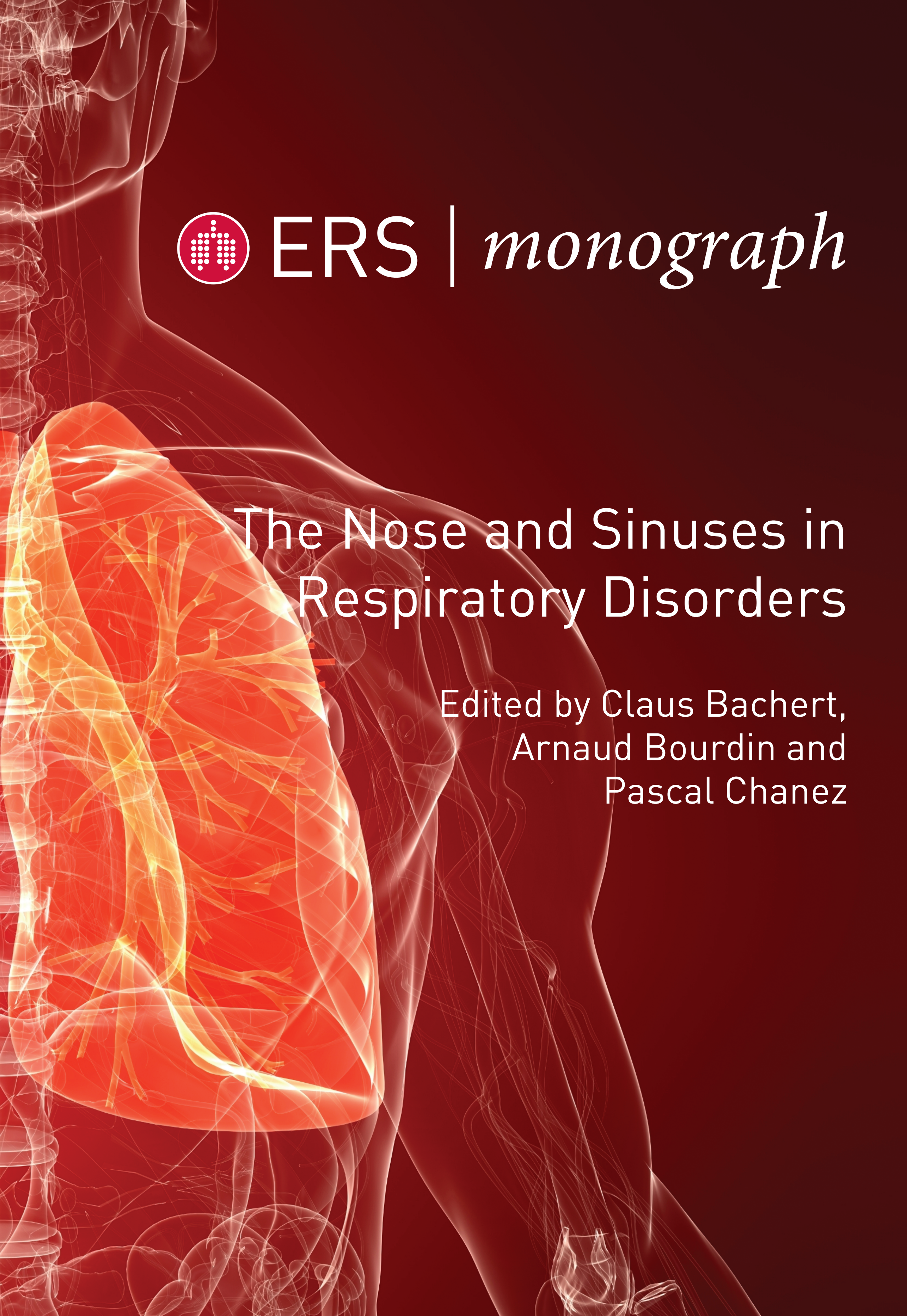

ERS | *monograph*

The Nose and Sinuses in Respiratory Disorders

Edited by Claus Bachert,
Arnaud Bourdin and
Pascal Chanez

The Nose and Sinuses in Respiratory Disorders

Edited by
Claus Bachert, Arnaud Bourdin
and Pascal Chanez

Editor in Chief
Robert Bals

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Preface

Robert Bals

The nose is an important body part for the pulmonologist. In my opinion there are three main reasons why lung doctors should read this *ERS Monograph* on "The Nose and Sinuses in Respiratory Disorders" and learn more about the role of the nose in lung diseases:

1) The nose represents the upper part of the airways and is thus an important component of the air conduction system. The "united airways disease" concept covers physiology as well as pathomechanisms. Thus, diseases of the lung are often diseases of the nose, and *vice versa*.

2) Lung-related symptoms may also originate from diseases of the nose and therefore the lung physician needs to know the basic concepts of nasal disorders, including diagnostic approaches that are available from their ENT colleagues.

3) Therapeutic interventions of diseases of the lung often include treatment of disorders of the nose.

With this *ERS Monograph*, we provide the reader with a broad and detailed overview on the basic biology of the interaction between the nose and the lung. The various chapters cover a number of diseases that involve both organs, *e.g.* cystic fibrosis, asthma, COPD and bronchiectasis, and the authors also discuss the effect of diseases of the nose on the lung. The focus is on the practical aspects of clinical work and providing insight into diagnostic procedures and therapeutic options in the ENT area.

The Guest Editors, Claus Bachert, Arnaud Bourdin and Pascal Chanez, have worked very successfully to select the topics and to integrate these aspects into this *ERS Monograph*, which summarises our current knowledge. I thank the Guest Editors and all of the authors of the individual chapters for their work on this excellent book. Together, they have produced a practical publication that comprises information on the scientific background and the application at the patient's bed. I am sure

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that this comprehensive overview will be useful for the clinical practice of a broad range of respiratory physicians and improve the care for patients with diseases of the nose and the lung.

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Guest Editors

Claus Bachert

Claus Bachert MD, PhD is chief of the clinic and Professor at the University Hospital of Ghent, Belgium, and also holds a position as Professor at the Karolinska Institute, Stockholm, Sweden. He qualified from the University of Heidelberg, Germany, and trained in ENT diseases and allergology in Mannheim and Düsseldorf, Germany. His research interests include the pathophysiology and management of diseases of the nose and sinuses, such as allergic and nonallergic rhinitis, chronic rhinosinusitis, and nasal polyposis. Specifically, he has worked on endotyping rhinosinusitis, innovative treatments such as biologicals for recalcitrant disease and the role of *Staphylococcus aureus* in the inflammation of nasal polyp disease.

He chairs the Upper Airways Research Laboratory at Ghent University and has published over 460 peer-reviewed articles in international journals. He has received several national and international prizes, and two doctor *honoris causa* (Capital University, Beijing, China and Democritus University, Thrace, Greece).

Claus Bachert forms part of the international guidelines groups ARIA (Allergic Rhinitis and its Impact on Asthma) and EPOS (European Position Paper on Sinusitis and Nasal Polyposis), has served on the Boards of the European Academy of Allergy and Clinical Immunology and World Allergy Organization, and was President (2007–2010) and Vice-President (2011–2016) of the German Allergy Society (DGAKI). He currently serves as an Associate Editor for the *Journal of Allergy and Clinical Immunology*.

Arnaud Bourdin

Arnaud Bourdin MD, PhD is head of pulmonology and a Consultant and Professor of Respiratory Medicine at Hôpital Arnaud de Villeneuve, Montpellier, France. He gained his MD and PhD in 2001 and 2006, respectively, from the University of Montpellier, and was subsequently a fellow at Monash University, Melbourne, Australia, working alongside Professor Tom Kotsimbos.

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He is head of a clinical research group investigating innovative treatments for asthma, COPD, idiopathic pulmonary fibrosis and pulmonary hypertension. His scientific research interests include COPD and severe asthma. He has acted as Principal Investigator for a number of trials in asthma and COPD, including the COBRA ("Cohorte Obstruction Bronchique et Asthme") study.

Arnaud Bourdin is an Organising Committee Member of the G2A project "Journées d'échange sur l'asthme sévère", and a member of the editorial team and reviewer for three international journals: *Respiratory Research*, *BMC Public Health* and *La Revue des Maladies Respiratoires*. He is also a member of the European Respiratory Society, at whose Congress he has acted as a Chair and speaker for the past 5 years. In addition, he is a credible speaker on the subject of severe asthma in France. He has authored or co-authored more than 100 peer-reviewed articles, reviews and monographs.

Pascal Chanez

Pascal Chanez MD, PhD, FERS is a Consultant and full Professor of Respiratory Medicine attending the "Clinique des bronches, de l'allergie et du sommeil et de la plateforme ambulatoire du pôle thorax" at the APHM and Aix-Marseille University, Marseille, France. He coordinates a research group at INSERM-CNRS U1067 in the same institute on the role of bronchial epithelium in inflammation and environmental aggression in severe bronchial diseases. He is the head of a clinical research group investigating new innovative treatments for severe asthma and COPD.

His clinical and research interests are devoted to a better understanding of the mechanisms of severe asthma and COPD with a special effort put into bringing clinical and biological findings together to provide patients with new specific biomarkers and therapies. He has demonstrated in the past his willingness and ability to gather researchers and clinicians together to decipher the complexity of severe asthma in France and Europe.

Pascal Chanez gained his MD and PhD degrees from the University of Montpellier and was a fellow at Imperial College London in the UK with Professor P.J. Barnes. He is the author or co-author of more than 300 peer-reviewed articles, reviews and monographs. He is an Associate Editor of the *European Respiratory Journal* and an Editorial Board Member of the *Journal of Allergy and Clinical Immunology.*

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Introduction

Claus Bachert[1,2], Arnaud Bourdin[3] and Pascal Chanez[4]

In 2001, the European Respiratory Society welcomed a *Monograph* entitled "The Nose and Lung Diseases" [1] and one of the original Guest Editors, Philippe Godard (1948–2011), was instrumental in gathering people around the idea that the nose is the most easily accessible part of the airways.

With this new *ERS Monograph* we would like to again emphasise the notion within our chest community that the nose and sinuses belong to the airway tree, and that it is part of our duty as chest clinicians to think about the upper airways in all our common diseases and to consider our ENT colleagues as important partners in improving the quality of life of our patients. The links between the upper and lower airways are numerous, including anatomical, physiological, triggers and risk factors. The presence of these strong relationships argues for a constant dialogue between specialists and we hope that the comprehensive overview presented in the various chapters herein will contribute to reinforce the willingness of our colleagues to undertake fruitful collaboration in order to increase our knowledge with the ultimate goal of improving patient care.

The first three chapters cover anatomy, imaging and clinical examination, within the approach of the "united airways" concept. This approach should consider a pragmatic understanding of the situation, subject to the constraints of human and financial resources, leading to the best compromise to establish a clear diagnosis. Mutual understanding between chest physicians and ENT specialists is the guiding principle. We should understand the real involvement of the upper airways in all chronic respiratory disorders and consider them as "morbidities" rather than comorbid conditions.

The association of nasal polyposis and asthma and the complex pathophysiological landscape is covered by chapters focusing on chronic infection and its potential impact on immunity, and the perspectives of both ENT and chest physicians. Sino-nasal involvement in cystic fibrosis and COPD patients requires specific attention, not only as a source of potential triggering pathways but also as a matter of persistent complaints. The subjective symptoms, including fatigue, impaired sleep quality, dyspnoea and mucus secretion, should direct more attention to the upper airways. Risk factors, triggers and other associated influences are important, but direct causality is often difficult to demonstrate and a strong

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research effort may lead to new evidence. The microbiome revolution is a potential source for a better understanding of the role of microorganisms in the inception, loss of control and natural history of chronic respiratory disorders from the nose to the alveoli.

The ultimate challenge is to improve the treatment for patients, and both chest and ENT physicians are relying on each other to understand and better control symptoms and the underlying disease as a whole. Little evidence has been provided so far to assess whether a single local intervention may be an option for curing persistent airways disease. The burst of biologics potentially active in both asthma and nasal polyposis provides perfect support for the "united airways" hypothesis.

In summary, we hope that this *ERS Monograph* will encourage chest physicians to consider upper airways disease seriously and to organise a common and constant dialogue with ENT surgeons to promote research, coordinate management and, ultimately, elicit new treatments for the best care of our patients.

> *La vapeur du tabac vous sort-elle du nez. Sans qu'un voisin ne crie au feu de cheminée?*
>
> *[That the tobacco-smoke spouts from your nose. Do not the neighbours cry "The chimney is afire"?]*
>
> *Cyrano de Bergerac [2]*

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2. Rostand E. Cyrano de Bergerac: A Play in Five Acts. 1897. Project Gutenberg 1254/1256. Available from: www.gutenberg.org Date last accessed: April 17, 2017.

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List of abbreviations

AERD	aspirin-exacerbated respiratory disease
ARS	acute rhinosinusitis
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane regulator
COPD	chronic obstructive pulmonary disease
CRS	chronic rhinosinusitis
CT	computed tomography
ENT	ear, nose and throat
FEV_1	forced expiratory volume in 1 s
GINA	Global Initiative for Asthma
IFN	interferon
IL	interleukin
ILC	innate lymphoid cell
MRI	magnetic resonance imaging
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
PCD	primary ciliary dyskinesia
QoL	quality of life
Th	T-helper
Treg	T-regulatory

Upper and lower airways: the same tissue?

Andriana I. Papaioannou[1], Clementine Bostantzoglou[2],
Chrysoula Kontogianni[2] and Mina Gaga[2]

The upper and lower airways form part of the respiratory system, conducting air in and out of the gas-exchanging units of the lungs. They share not only this function but also many histological characteristics and immune mechanisms, and many diseases affect both the upper and lower airways. However, the nose and lungs also have distinct functions and, importantly, they are managed by different physicians. Because of the frequent coexistence of disease all along the respiratory tract, as is the case with upper and lower respiratory tract infections or with asthma and rhinitis, it is important to be aware of the similarities between the two systems and the impact they have on each other.

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The nose and the lungs are anatomically and physiologically closely related organs. The nose plays an important role in the conducting and conditioning of inhaled air, vocal resonance, olfaction, nasal resistance, ventilation and drainage of the sinuses, and protection of the lower airway. Protective defence mechanisms include sneezing, mucociliary clearance and filtering of small particles, as well as immunological cells and mediators [1]. However, in addition to their central role in gas exchange, the lungs also have various important homeostatic functions, including defence mechanisms, lipid metabolism, blood–endothelium interactions and mediator production [2]. Apart from their obvious anatomical connection which allows air to pass into and out of the lungs, the upper and lower airways share histological and immunological similarities and functional complementarity; thus, during recent years, there has been a trend for the airways to be seen as an integrated system, referred to as the "unified (or "united") airways model" [3]. This model proposes that the airways respond to various stimuli in a similar way and have common disease mechanisms. This concept has mostly been studied in allergic inflammation, and there is evidence that not only asthma and rhinitis coexist but that the immune response in the upper and lower airways is similar. There is less evidence for this

---

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hypothesis in COPD, in infections or in systemic diseases, although some data do exist. In this chapter, the anatomy, histology and the basic mechanisms of response to immunogenic stimuli in the nose and the lungs are briefly described.

Anatomy

The respiratory tract is functionally divided into the conducting part and the gas-exchanging part. The conducting airways are anatomically subdivided into the nose and mouth, pharynx, larynx, trachea, and the bronchi, which keep branching down to the level of the respiratory bronchioles. The respiratory bronchioles, with the corresponding alveoli, represent the gas-exchanging part of the lungs (figure 1).

The upper respiratory tract extends from the external nares (nostrils) and the mouth to the larynx; the lower respiratory tract extends from the larynx to the alveoli. The nasal cavity is surrounded by bone and divided into two halves by the nasal septum. Therefore, the upper airway starts as two separate airways which extend from the anterior nares through the nasal vestibules, which are trumpet-shaped orifices narrowing towards the main nasal cavity and there they are united to form a single airway (at the level of the nasopharynx). The junction between the vestibules and the main nasal cavity is called the nasal valve or internal ostium, and is the narrowest point of the airways. At this point the area of the airways is just 0.3 cm^2, expanding to nearly 1.3 cm^2 in the main cavity [4]. In the main nasal cavity, three bony shelves project from the lateral wall on each side: the nasal turbinates or conchae. The turbinates increase the surface of the nose while at the same time they narrow the lumen (figure 2). This design facilitates close contact of inhaled air

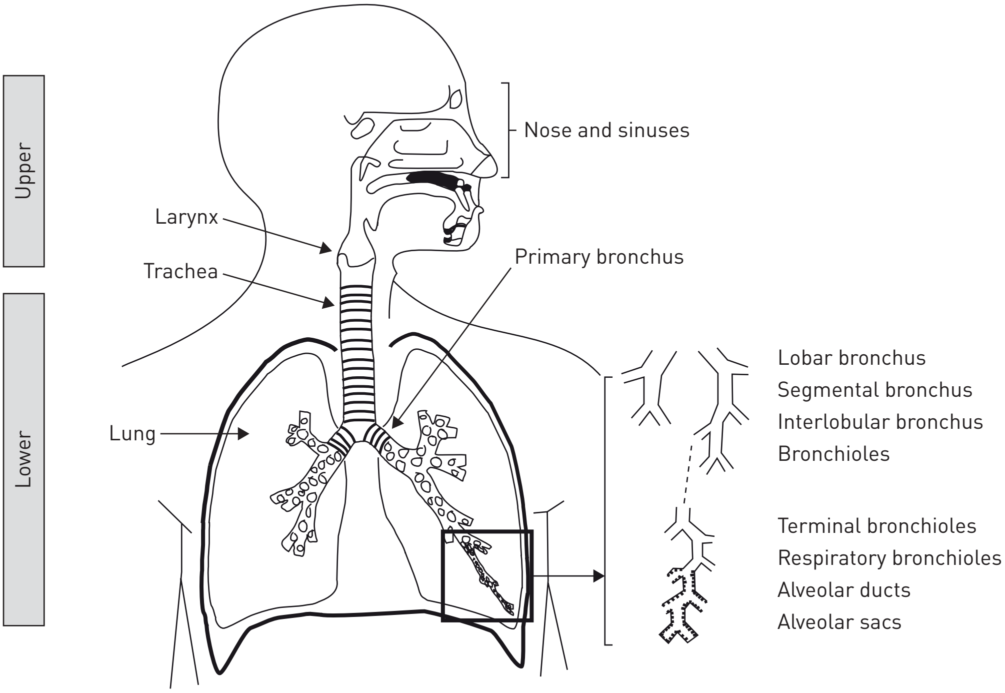
Upper
Lower
Nose and sinuses
Larynx
Trachea
Primary bronchus
Lung
Lobar bronchus
Segmental bronchus
Interlobular bronchus
Bronchioles
Terminal bronchioles
Respiratory bronchioles
Alveolar ducts
Alveolar sacs

Figure 1. Cross-section of the airways. Reproduced and modified from [8] with permission from the publisher.

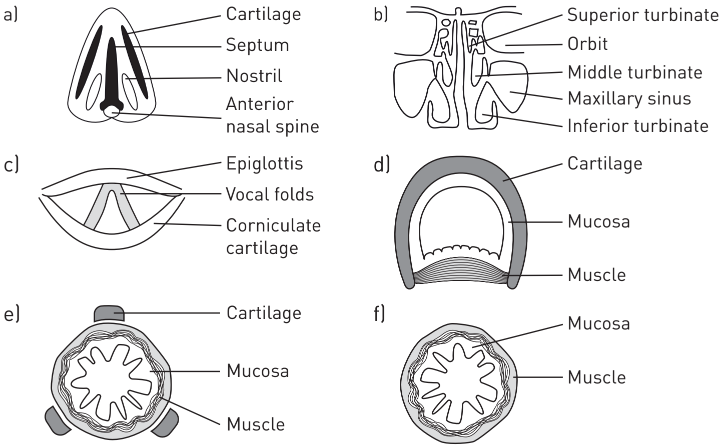
a)
Cartilage
Septum
Nostril
Anterior nasal spine
b)
Superior turbinate
Orbit
Middle turbinate
Maxillary sinus
Inferior turbinate
c)
Epiglottis
Vocal folds
Corniculate cartilage
d)
Cartilage
Mucosa
Muscle
e)
Cartilage
Mucosa
Muscle
f)
Mucosa
Muscle

Figure 2. Schematic cross-sections of the airways: a) internal ostium of the nose, b) nasal/paranasal cavities, c) larynx, d) trachea, e) bronchus and f) bronchiole. Not to scale. Reproduced and modified from [8] with permission from the publisher.

with the nasal mucosa, and promotes humidification and heating of the air. The shape of the nasal airway, with its bends and differences in lumen area, causes turbulent flow of the air that not only facilitates heat and humidity conditioning, but also promotes deposition and trapping of particles on to the nasal mucosa. As a result, the air that enters the lower airways is filtered and conditioned [5]. A small region (the olfactory region) in the upper part of the nasal cavity is dedicated to smell. The nasal cavity is surrounded by the paranasal sinuses, which communicate with it by small apertures 2–6 mm in diameter, and help voice resonance and possibly heat/cold insulation (figure 3) [6].

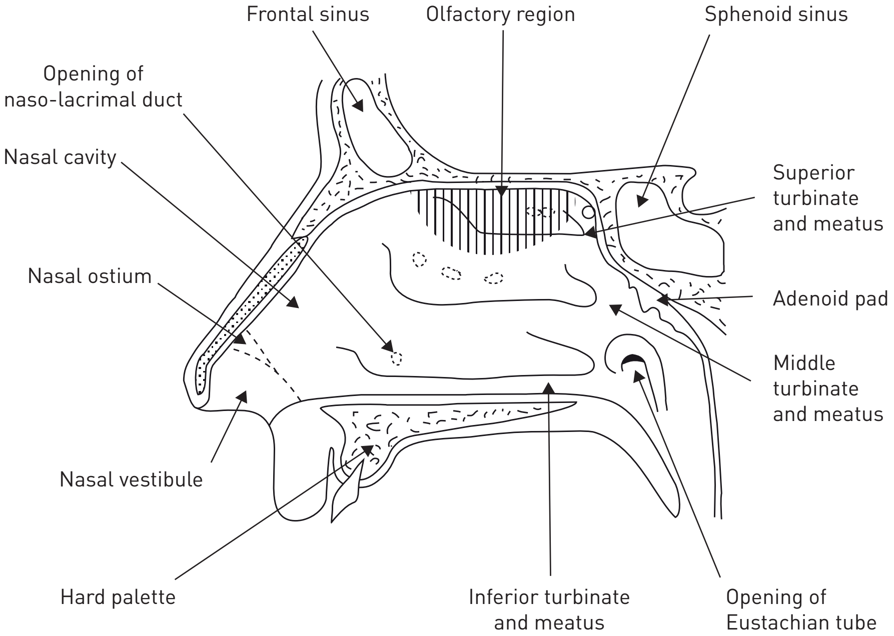
Frontal sinus
Olfactory region
Sphenoid sinus
Opening of naso-lacrimal duct
Nasal cavity
Superior turbinate and meatus
Nasal ostium
Adenoid pad
Middle turbinate and meatus
Nasal vestibule
Hard palette
Inferior turbinate and meatus
Opening of Eustachian tube

Figure 3. Lateral wall of the nasal cavity. Reproduced and modified from [8] with permission from the publisher.

Following the nose is the pharynx, containing the openings of the Eustachian tubes, the adenoids and the tonsils. Below the pharynx is the larynx. The larynx is the second narrowest part of the airway. It is the organ of phonation and also acts as a valve that protects the lower airways and the lungs. The laryngeal mucosa is loosely bound to the supporting cartilage so oedema fluid can easily accumulate. Severe laryngeal oedema can be life threatening and it is usually the result of allergen exposure in sensitive individuals or of viral infections in children. The laryngeal lumen may also become obliterated during laryngeal spasm due to a strong reflex reaction of the laryngeal muscles [7].

The trachea begins below the larynx and is supported by irregular rings of cartilage, which are incomplete dorsally. The cartilage prevents the trachea from collapsing when intrathoracic pressure increases. However, during cough, when there is a steep rise in intrathoracic pressure, the dorsal wall of the trachea protrudes into the lumen, narrowing it considerably. The length of the trachea is 10–12 cm; about half of it is extrathoracic and half intrathoracic. At its distal end, it bifurcates into the two main (primary) bronchi. The main bronchi also have shaped cartilaginous rings to support them. The main bronchi divide and form segmental bronchi which keep branching to form smaller generations of bronchi and bronchioles (figure 1). Eight to 23 generations of airway can exist from the trachea to the alveoli. As the bronchi become smaller and more distal, cartilage becomes scarce; no cartilage is found in the bronchioles. The conducting airways end at the terminal bronchioles. Distal to these, respiratory bronchioles and alveoli are present, and constitute the gas-exchanging part of the lung [8].

Histology

Structure of the upper and lower airways

Although there are some exceptions (*e.g.* the keratinised epithelium of the anterior nares and the stratified squamous epithelium of the nasopharynx and larynx) [9], the histological characteristics of the normal nasal and bronchial mucosa are very similar, and both the upper and lower respiratory tracts, all the way from the nose and paranasal sinuses, through the trachea and larynx, to the distal bronchioles, consist of common structures such as the ciliary epithelium, basement membrane, loose connective tissue (lamina propria), glands and goblet cells, which form the basis of the so-called “united airways” (figure 4) [10, 11]. Blood vessels, fibroblasts, nerves, mucous glands and immune cells are situated beneath the epithelium in the subepithelium and submucosa [9]. Differences between the upper and lower respiratory tract include the greater number of subepithelial capillaries and the venous sinusoids which can be observed in the nose, and the presence of smooth muscle cells which extend from the trachea to the terminal bronchioles, and are found in the upper respiratory tract [9]. It is now widely recognised that local and systemic effects which lead to reactions throughout this system, and pathophysiological processes resulting from these effects, exert similar responses in both the upper and lower airways [3].

The airway epithelium is composed of a variety of cells, such as nonciliated columnar cells, basal cells, ciliated cells, goblet cells and neurosecretory cells (Kulchitsky, amine-containing or APUD (amine precursor uptake and decarboxylation) cells) [9]. Each cell plays a specific role in the structure and function of the respiratory tract. The basal cells are the stem cells for the epithelial layer. In response to injury, during the repair procedure, basal cells proliferate and migrate to damaged sites where they differentiate in order to restore all cell

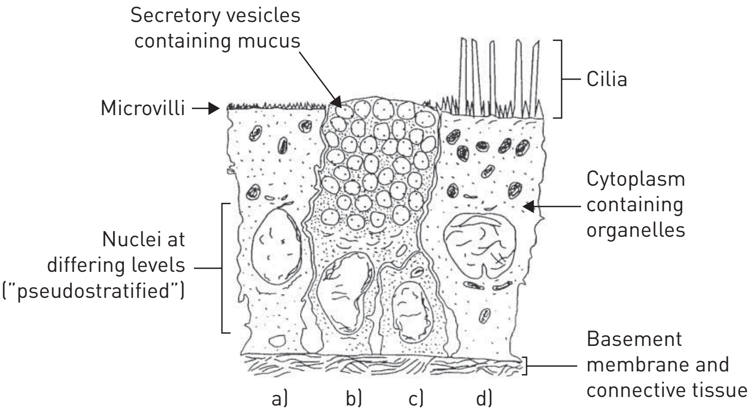
Secretory vesicles containing mucus
Cilia
Microvilli
Cytoplasm containing organelles
Nuclei at differing levels ("pseudostratified")
Basement membrane and connective tissue
a)
b)
c)
d)

Figure 4. The four common cell types in airway epithelium: a) nonciliated columnar cells, b) goblet cells, c) basal cells and d) ciliated columnar cells. See main text for more details. Reproduced and modified from [8] with permission from the publisher.

types [10, 12]. Chronic inflammatory airway diseases are often associated with hyperproliferation of basal cells followed by squamous differentiation, leading to the development of an abnormal epithelium [13]. The main role of ciliated cells is moving the mucus blanket towards the upper respiratory tract. There are approximately three to five ciliated cells for every mucous cell [9], whereas 50–80% of epithelial cells lining the airways are ciliated, which makes them the predominant cell type within the human airways [10]. Ciliary cells have also been reported to be involved in epithelial cell transdifferentiation and repair [14]. Mucus-producing goblet cells are present within the epithelium all the way from the upper to the lower respiratory tract, although they disappear in the respiratory bronchioles as the surfactant-rich club cells appear [13].

The basement membrane of the respiratory tract is composed of collagen type I, III and IV fibrils. Below this membrane, there is an almost cell-free zone composed of fibronectin and collagen type III and V, and a submucosal layer consisting of glands, inflammatory and interstitial cells, nerves, and vessels. Three types of glands can be observed in this area: mucous, seromucous and serous glands. In normal subjects, the cells in both the nasal and airway mucosa are mostly lymphocytes, macrophages and mast cells, which are interspersed by fibroblasts [9, 15].

Functional role of the upper and lower airways

In addition to its structural role, the airway epithelium serves as the first line of defence of the respiratory system as it is widely exposed to the external environment. Thus, the airway epithelium not only provides a physical barrier against bacteria, viruses and air pollutants, but is also actively involved to the innate and adaptive arms of the immune system *via* mucus secretion, and production of immunoglobulins, pro-inflammatory cytokines, neuropeptides, endothelin, nitric oxide, transforming growth factor-β and arachidonic acid metabolites [10]. Dysregulation of these defence mechanisms is related to the pathogenesis of several respiratory diseases [16].

The main first line of defence of both the upper and lower respiratory tract is mucociliary clearance, which depends on the function of ciliated and secretory cells. The mucus that is produced by the goblet cells traps inhaled materials which are then pushed towards the respiratory system cephalad to the nasopharynx by the cilia, situated at the apical cell surface of the ciliated cells [10]. The cilia are microtubule-based cell organelles on the luminal surface of the cell extending from the basal body, which is a centriole containing an axoneme [10]. The axoneme, which actually forms the microtubule cytoskeleton of the cilium, consists of a ring of nine doublet microtubules surrounding a central pair ("9+2"). There are approximately 200–300 cilia per cell. Each one has a diameter of 0.2–0.3 μm and a length ranging from 6–7 μm in the upper airways to 4 μm in the smaller airways [17]. The cilia beat at a rate of 12–16 strokes$\cdot$s^{-1} in a steady direction and in a harmonised fashion, generating a wave-like movement across the epithelial surface [18]. The necessary force for the motility of each microtubule doublet is generated by the inner and outer dynein arms, and is affected be the levels of cAMP and cGMP, and the intracellular calcium concentration, pH and bicarbonate [10].

During the cilia beat, the forward stroke of the cilia is rapid and powerful to allow penetration into the mucus layer and towards the nasopharynx where the mucus can be either expectorated or swallowed [19]. The effective movement of the mucus towards the epithelial layer depends on several factors, *e.g.* level of hydration, mucin production by the secretory cells and coordinated function of the ciliated cells [17]. Numerous microvilli are present in the apical surface of the ciliated cells and also contribute to the transepithelial movement of fluid and electrolytes. Cilia dysfunction linked to respiratory diseases is most commonly related to problems within the dynein arms and in these cases the defence capacity of the epithelium is significantly reduced [17]. Numerous ciliary proteins have been identified; however, their exact role still remains unknown. The cilia membrane that is connected to the cell membrane contains specific receptors and ion channel proteins which contribute to several signalling pathways, control motility and react to various mechanical or chemical stimuli [10]. Cilia function (*i.e.* beat frequency and/or wave form), motility, structure (length of the cilia), response to endogenous or exogenous factors and extent of ciliated areas might be influenced during airway diseases [10].

Impaired mucus clearance from the sinus and nasal epithelium leads to stasis of secretions, making the host susceptible to bacterial infection, and this results in neutrophilic inflammation and CRS. In the same way, impaired mucus clearance from the lower respiratory tract leads to chronic bacterial colonisation and inflammation, which finally results in the development of bronchiectasis. This is the reason why patients present with both rhinosinusitis and bronchiectasis in cases of cilia dysfunction [19].

In addition to mucociliary clearance, other important host defence mechanisms of the respiratory tract include immunoglobulins, as well as defensive components (*e.g.* chemokines and cytokines) and antibacterial peptides of the mucus (*e.g.* lysozyme). All of these elements contribute to prevent possible harmful organisms from entering the body [19, 20].

Serous glands situated in the submucosal layer of both the upper and lower airways are able to produce secretory IgA, which is an important component of mucosal immunity [15, 21]. Furthermore, despite the fact that lymphocytes are rare in the normal airway lumen, they can be found in the submucosal layer of the airway tract where a part of their role is related to the production of IgA [21]. The recognition of specific IgA receptors on the surface of blood leukocytes and alveolar macrophages has provided a novel possible mechanism of interaction between the cellular and humoral immune systems, showing that IgA in the mucosal fluids can also interact with phagocytic cells [21].

Airway epithelial cells also express different types of receptors such as Toll-like receptors (TLRs), protease-activated receptors, nucleotide-binding oligomerisation domain (NOD)-like receptors and C-type lectin receptors [20]. TLRs are a family of proteins involved in the recognition of microorganisms. The TLR signalling cascade helps to initiate biological and physiological responses towards a recognised pathogen, resulting to the production of a vast array of cytokines/chemokines that are produced by antigen-presenting cells, dendritic cells, T- and B-lymphocytes, and macrophages, thus contributing to the induction of the immune response [22]. NOD-like receptors are mainly expressed in the epithelium and are induced by bacterial stimuli; they seem to be involved in the clearance of numerous bacterial pathogens [20]. Finally, C-type lectin receptors are a family of proteins which recognise the β-glycans present on fungi, yeast and mycobacterial cell walls, contributing to the defence against these organisms [20].

Neural supply and reflexes

The neural supply to the nose is sensory and autonomic. Sensory innervation is supplied by two branches of the trigeminal as well as the ophthalmic, maxillary and olfactory nerves. The trigeminal nerve provides the sensation of touch, pain, hot, cold, itch and nasal airflow, and also detects certain chemicals and organic substances (*e.g.* ammonia, sulphur dioxide, acetone and menthol). The olfactory region acts as long-distance chemoreceptor sensing odorants contained in inspired air and enabling the sense of smell.

Efferent neural supply is both parasympathetic and sympathetic. Parasympathetic fibres innervate glands and sympathetic fibres control nasal blood flow [23, 24]. In addition to adrenergic and cholinergic transmission, a number of neuropeptides have been found in the nasal mucosa [25, 26]. Parasympathetic nerve endings release vasoactive intestinal peptide (VIP) and peptide histidine–methionine (PHM), both potent bronchodilators. Sympathetic nerve endings release neuropeptide Y, and unmyelinated C fibres release tachykinins, calcitonin gene-related peptide (CGRP), neurokinin A (NKA) and gastrin-releasing peptide. Substance P is often found as a cotransmitter with CGRP and NKA.

Mechanical, chemical or physical irritation of the nasal mucosa may induce reflex reactions. Mild stimuli result in sneezing and nasal hypersecretion *via* the trigeminal nerve [27]. Stimulation may also lead to neurogenic inflammation through inflammatory mediators such as substance P, NKA and CGRP. Potent reflex respiratory and cardiovascular responses may also be induced after trigeminal nerve stimulation, and include closure of the larynx, bradycardia and apnoea.

The lungs receive parasympathetic innervation from the vagus nerve and sympathetic innervation from the upper thoracic ganglia. Innervation is both sensory (afferent) and autonomic (efferent). Sensory nerves probably begin as free endings but may be associated with specific bronchial cells as neuroepithelial bodies. There are three types of sensory receptors: type I (cough and irritant receptors), type II (stretch receptors) and type III (C fibres, J receptors) [28]. Stimulation of sensory nerves causes various reflex reactions, including cough, bronchoconstriction, hyperventilation, mucus release, bradycardia, hypotension and neurogenic inflammation. Autonomic nerves have both excitatory and inhibitory function, and control bronchial smooth muscle, mucus-secreting cells and vasculature. Bronchial smooth muscle is innervated by the vagus. As in the nose, various noncholinergic, nonadrenergic mediators play an important role as neurotransmitters in the lung. Neuropeptides found in the bronchial wall include bronchodilators (VIP and PHM), pro-inflammatory bronchoconstrictors (substance P, NKA and CGRP) and a potent vasoconstrictor (neuropeptide Y). Neuropeptides may be released from sensory nerves on retrograde activation through a local reflex mechanism. Neural reflexes are more pronounced when there is inflammation of the airways [8].

Triggers resulting in upper and lower airway morbidity

Various triggers are noxious to or cause damage to the respiratory system and induce inflammatory reactions. These triggers include viruses and bacteria, allergens, smoke and noxious gases, organic and nonorganic dusts and particles (as discussed in more detail by Xepapadaki *et al.* [29] and Charpin and Caillaud [30] elsewhere in this *ERS Monograph*). As the whole airway is exposed to the environment through the air that is inhaled, reactions can be expected all along its length, whether in the upper or the lower system, and this has been documented in many studies, mainly in asthma and rhinitis [31, 32]. COPD is associated with significant sino-nasal symptoms, inflammation and airway obstruction that impair QoL, and the severity of upper airway involvement relates to that present in the lower airway. Moreover, relationships between upper and lower airway bacteria and inflammation, and the association between sinusitis and treatment failure at exacerbation, raise the possibility that nasal intervention in COPD may not only improve health status, but may also affect important clinical outcomes such as exacerbation frequency [33, 34]. Further evidence that the respiratory system responds in a similar fashion all along its length comes from studies of epigenetic changes, which show that nasal epithelial cells are suitable to analyse DNA methylation in human diseases primarily affecting the lower airway tract [35].

When a pathogen or any trigger that is recognised as dangerous enters a tissue, or in the case of the respiratory tract comes into contact with the respiratory mucosa, bypassing the mechanisms of sneezing, coughing and mucociliary clearance, it needs to be eradicated and an immune reaction is mounted. An antigenic stimulus stimulates both innate and adaptive immunity. Cells are recruited and activated, and mediators are released to kill/extinguish the pathogen/trigger. In this process, not only the trigger but also the tissue will be damaged, due to the enzymes and mediators released during the inflammatory reaction. A repair process will then have to begin to restore the tissue.

Each step of an immune reaction can be derailed. The pathogen may not be recognised, as happens in immune deficiencies, and no reaction is mounted or a weak reaction is seen. Conversely, as in allergy or autoimmunity, a strong inflammatory reaction that is misplaced or not necessary may be mounted to a nonpathogen or to self-antigens, leading to symptoms and causing damage. Various mechanisms, such as apoptosis, reduce the tissue damage caused by inflammatory cells. Nevertheless, the tissue is usually damaged and damage is normally followed by a repair process that leads to reconstruction of normal tissue. However, in cases of chronic damage, repair processes are interrupted and this leads to permanent changes in the tissue structure and different types of fibrosis. These changes are more pronounced in the bronchi than they are in the nose, and they can be observed in cases of chronic bronchitis and bronchiectasis, as well as in asthma (where they are called "remodelling"). Similarly, inflammation and structural changes can be seen in systemic disease such as CF.

Upper and lower airway interactions

The upper and lower respiratory tracts seem to communicate *via* direct and also more indirect mechanisms such as neural and systemic pathways. Numerous studies indicate that impairment of the functions of the nose has consequences for the lower airways as well. More specifically, it has been shown that an antigen placed in an area of the respiratory tract results in induction of inflammatory mediators in other distal areas [36], leading to the conclusion that onset of inflammation can occur throughout the respiratory system by some regulatory processes which seem to be triggered from any site of the respiratory tract [3]. The pathophysiological mechanisms that could explain the interaction between the nose and the lung are: pulmonary aspiration, neural reflex mechanisms, and systemic induction of inflammatory mediators and cells [3]. In clinical practice, the need to understand this upper and lower airway interaction has been recognised by physicians. Moreover, the nose is the first barrier to environmental assaults; it filters and humidifies the air that enters the lower airways, making it less damaging to the lower airways and the lungs. It therefore becomes clear that treating the nose and keeping it healthy and functional is pivotal in controlling lung pathology. This is discussed further by Doulaptsi *et al.* [37] and Scadding and Scadding [38] in the context of the "united airways model" elsewhere in this *ERS Monograph*.

Conclusions

Available data suggest that the upper and lower airways are not only anatomically and physiologically closely related and respond in a similar way, but also have functional and inflammatory interactions *via* neural and systemic pathways. The epithelium of both the upper and lower airways serves as the first line of defence of the respiratory system and, when damaged, leads to inflammatory reactions that can be triggered from any site of the respiratory tract and occur throughout the respiratory system. Our understanding of this interaction of the upper and lower airways has led to the recognition of the fact that it is necessary to examine the whole of the respiratory system and, when needed, treat both the upper and lower airways in a "united airways model". Moreover, as the nose is the first contact with the ambient air and the environment, and its obstruction through inflammatory and reflex mechanisms exposes the lower airways to more stimuli, it is important to treat the nose and keep it functioning effectively in order to control diseases of the lung. The association of the upper airways with specific respiratory disorders, such as CF, infections and exacerbations of chronic diseases, CRS and asthma, COPD, non-CF bronchiectasis, and PCD, is discussed in depth in other chapters throughout this *ERS Monograph* [39].

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Chapter 2

How to explore the nose in respiratory disorders in 2017: a one-stop clinic?

Laurent Guilleminault[1], Guillaume de Bonnecaze[2], Elie Serrano[2] and Alain Didier[1]

Epidemiological and clinical studies show the high frequency of clear associations between upper and lower airways disorders. Chronic inflammatory processes that affect the upper airways can participate in the worsening of bronchopulmonary disease and contribute to impaired QoL. Thus, physicians that manage respiratory diseases need to evaluate common rhinological problems. In daily practice, examination of the nose mainly relies on meticulous questioning followed by a complete clinical examination of the upper respiratory tract. Practitioners can perform anterior rhinoscopy using a frontal lamp and a speculum or an otoscope (with a nasal adapter) before and after vaporisation of a topical vasoconstrictor. This first step may be followed, if necessary, by flexible or rigid nasal endoscopy that requires specialised instrumentation and medical experience. Other examinations, such as rhinomanometry, nasal cytology, mucociliary function or an olfactory examination, are conducted less frequently, and depend on the data obtained during questioning of the patient and subsequent examinations.

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Epidemiological and clinical studies show a high frequency of coexistence of upper and lower airways dysfunction, and clear associations between disorders of the two parts of the respiratory tract. Chronic inflammatory processes that affect the upper airways interact with the lower respiratory tract through several mechanisms [1, 2]. The concept of "united airways disease" has recently emerged [3], where the upper and lower airways are considered a unified morphological and functional unit. Upper and lower airways diseases, particularly rhinitis and asthma, have similar epidemiological, pathophysiological and clinical characteristics [4]. Allergic rhinitis and allergic asthma

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are characterised by a similar inflammatory pattern, in which eosinophils and T-lymphocytes are the predominant cells [3]. AERD is characterised by the presence of chronic sino-nasal inflammation and nasal polyps [5]. Both respiratory tract and polypoid tissue from patients with AERD have shown eosinophilic infiltration and activation with the presence of eosinophilia [6]. Defining the nature of upper airway involvement can help the physician correctly address new approaches to asthma investigation and treatment.

At a clinical level, upper airway inflammation may worsen a bronchopulmonary disease and impair QoL. However, in many instances, patients with both upper and lower airway pathologies have predominant symptoms at one site and so may neglect to report symptoms that affect other sites. Physicians that manage respiratory diseases should evaluate common rhinological problems to ensure that patients receive an overall therapeutic approach.

Physical examination of a patient with a nasal pathology is only considered after meticulous questioning. This can often orient a diagnosis relatively accurately and guide the choice of possible complementary examinations. Although nasal endoscopy is the key step in diagnosis, a complete clinical examination of the nasal pyramid, the orbital region, the occlusion and buccal cavity should not be neglected, together with a thorough ENT examination.

The development of miniaturised optical systems with a light source has enabled exploration of the nasal cavities [7, 8]. However, nasal endoscopy is not only visual, but also includes palpation of the mucosa, and can be combined with bacteriological, cytological and histopathological sampling to further refine a diagnosis. The need for further exploration then depends on data obtained during questioning of the patient and the results from nasal endoscopy.

Tools available to investigate the nose and their usefulness to chest physicians and ENT specialists are summarised in table 1 and figure 1.

Table 1. Tools available to investigate the nose and their usefulness to chest physicians and ENT specialists

	Chest physician	ENT specialist
Questioning the patient	+++	+++
Anterior rhinoscopy	+++	+++
Posterior rhinoscopy	+	++
Nasal endoscopy	+[#]	+++
Rhinomanometry	+	+++
Peak nasal inspiratory flow	+++	+++
Acoustic rhinometry	+	+++
Exploration of mucociliary function	+	+++
Cytology exploration[¶]	+++	+++

+++: easy to perform; ++: quite easy to perform; +: hard to perform. [#]: requires a flexible endoscope; [¶]: depends on the cytopathologist's expertise.

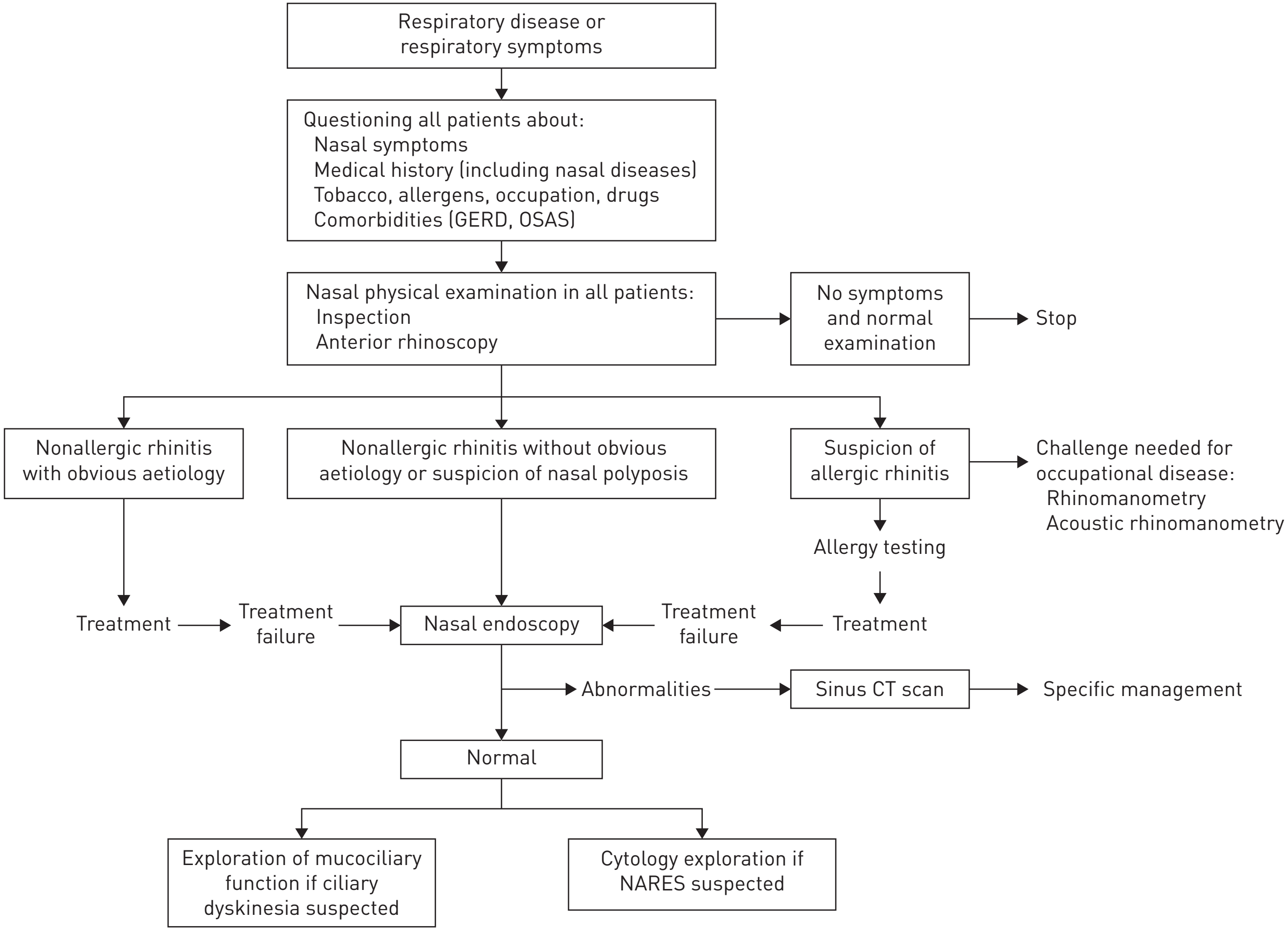
Respiratory disease or respiratory symptoms
Questioning all patients about:
Nasal symptoms
Medical history (including nasal diseases)
Tobacco, allergens, occupation, drugs
Comorbidities (GERD, OSAS)
Nasal physical examination in all patients:
Inspection
Anterior rhinoscopy
No symptoms and normal examination
Stop
Nonallergic rhinitis with obvious aetiology
Nonallergic rhinitis without obvious aetiology or suspicion of nasal polyposis
Suspicion of allergic rhinitis
Challenge needed for occupational disease:
Rhinomanometry
Acoustic rhinomanometry
Allergy testing
Treatment
Treatment failure
Nasal endoscopy
Treatment failure
Treatment
Abnormalities
Sinus CT scan
Specific management
Normal
Exploration of mucociliary function if ciliary dyskinesia suspected
Cytology exploration if NARES suspected

Figure 1. Decision tree classifying the different techniques used to explore the nose in patients with respiratory disease or respiratory symptoms. GERD: gastro-oesophageal reflux disease; NARES: nonallergic rhinitis with eosinophilic syndrome; OSAS: obstructive sleep apnoea syndrome.

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Information gathering

The patient's medical history

As for a lung examination, the first step in examining the nose is to collect functional signs and the patient's medical history. In the European Academy of Allergy and Clinical Immunology position paper that describes the diagnostic tools used in rhinology, the authors highlight the importance of determining a patient's history so that, when rhinitis or rhinosinusitis occurs, "an accurate history is usually more important than any other investigation" [9]. This remains essential when investigating the nose of a patient with a respiratory disease.

Functional signs

Involvement of nasal symptoms in allergic and nonallergic asthma has been clearly established [10]. In one study, it was estimated that the prevalence of nasal symptoms affected 46% of asthmatic patients [11]; these patients had worse asthma control, greater exacerbation and worse QoL than those without nasal symptoms [12]. In COPD, the prevalence of nasal symptoms can be lower, but such symptoms are often present in COPD patients (~25%) who report having rhinitis and/or rhinosinusitis [13]. COPD patients with nasal symptoms constitute a specific group of patients with chronic bronchitis. The dominant usual clinical signs are nasal obstruction, rhinorrhoea and sneezing. Other functional signs may include post-nasal drip, coughing, breathing problems, itching of the nose, palate and eyes, headache, facial pain, and olfactory disorders [14]. Watery nasal catarrh, a nasal obstruction, sneezing and itching are all risk factors for asthma (odds ratio 1.61 (95% CI 1.26–2.06), 1.85 (95% CI 1.4–2.32), 1.66 (95% CI 1.27–2.17) and 1.71 (95% CI 1.30–2.26), respectively) [11].

Nasal obstruction in chronic rhinitis is usually bilateral, or can alternate from nostril to nostril, and is affected by decubitus. It may be of minor intensity, with no effect on a patient's activity, or can considerably impede physical effort and cause difficulties in sleeping. Indirect signs of nasal obstruction should be sought, such as dry mouth, dry cough, pharyngeal pain, repeated tracheobronchitis, chronic tubal catarrh and increased nocturnal snoring. A local architectural or tumoral cause must always be suspected when a nasal obstruction is unilateral.

Rhinorrhoea may occur on its own or in association with other symptoms. It may be aqueous, serous or purulent, in which case superinfection is probable and should be investigated. Sneezing usually occurs in bouts, and there is a significant relationship between sneezing intensity and rhinorrhoea [14]. Post-nasal drip produces the sensation of a foreign body in the pharynx and a burning or tickling sensation in the throat, but is sometimes hard to recognise on examination [15]. Itching and burning of the nose, palate and eyes is mainly encountered in hay fever. Olfactory disorders, such as hyposmia or anosmia, are sometimes associated with taste disorders, in which case involvement of the sinus should be suspected [16]. Headaches and facial pain are reported in ~30% of cases of rhinitis, but are not necessarily correlated with sinus abnormalities and lung diseases [17].

Personal and family medical history

A patient's medical history should include information on possible surgical antecedents, personal allergies, allergies within the family and any facial trauma. A family history of atopy is a clear risk factor for allergic rhinitis and asthma [18]. Any previous or current treatments should be noted. The effect of any previous treatments for nasal symptoms should be investigated in order to determine if the therapy received is impacting on the present symptoms. Physicians should be careful regarding the misuse or overuse of α-agonists. Sympathomimetic α-adrenoceptor agonists, due to their vasoconstrictor action, can directly target the underlying vascular features, thus driving nasal obstruction [19]. Prolonged utilisation of this medication can lead to serious adverse reactions, such as central neurological effects (essentially consisting of headache, seizures, stroke, *etc.*), cardiovascular adverse reactions (including hypertensive crises), tachycardia or palpitations and rebound congestion, which is defined by deterioration of the feeling of nasal congestion after stopping α-agonist therapy [20]. Short-term use could be discussed in the acute forms, but this medication should not be prescribed in the chronic condition (*i.e.* CRS).

A full list of a patient's medications should be available to the physician to enable a potential diagnosis of drug-induced rhinitis [21]. The main drugs involved in drug-induced rhinitis are listed in table 2. The link between nasal and respiratory symptoms and the use of aspirin or NSAIDs should be investigated to evaluate AERD. Rhinitis associated with AERD usually develops during the third decade with concomitant onset of nasal congestion, hyposmia and chronic rhinorrhoea, and can progress to CRS with or without nasal polyps [22].

Environmental factors

The nose is the first part of the respiratory tract to have contact with the environment. Environmental factors can have a negative impact on nose functionality and may play a key role in the nasal symptoms of patients with a bronchopulmonary disease.

Exposure to tobacco

Exposure to smoking tobacco is one of the main factors that has a negative impact on the nose and lungs. In asthma, tobacco smoking is clearly associated with an accelerated

Table 2. Main drugs involved in drug-induced rhinitis

Mechanism	Drugs
Local inflammatory type	Aspirin, NSAIDs
Neurogenic type	Centrally acting sympatholytics: clonidine, methyldopa, moxonidine, rescinnamine, rilmenidine Ganglion blocking sympatholytics: trimethaphan Peripherally acting sympatholytics: prazosin, guanethidine, indoramin, doxazosin, phentolamine Vasodilators/phosphodiesterase type 5 inhibitors: sildenafil, tadalafil, vardenafil
Idiopathic (unknown) type	Antihypertensives: amiloride, angiotensin-converting enzyme inhibitors, oral β-blockers, calcium channel blockers, intraocular or ophthalmic preparations of β-blockers, chlorothiazide, hydralazine, hydrochlorothiazide Hormones: exogenous oestrogens, oral contraceptives Psychotropics: chlordiazepoxide–amitryptyline, chlorpromazine, risperidone, thioridazine Other: gabapentin

Information from [21].

decline in lung function, more severe symptoms, impairment to QoL and diminished therapeutic response to steroids [23]. Its impact on CRS has been also demonstrated [24].

In patients with allergic rhinitis, smoking has been significantly related to the risk of incident asthma [25]. Active and passive exposure to smoking is associated with allergic rhinitis, and this association is stronger for adolescents and children [26]. Exposure to smoking not only impacts on asthma and allergic rhinitis, but also increases the risk of nonallergic rhinitis in adults [27]. Interestingly, nasal symptoms, provoked by exposure to tobacco smoke, predicted COPD with an odds ratio of 2.5 (95% CI 1.4–4.2) [28]. The role of passive inhalation of tobacco smoke and the occurrence of recurrent respiratory infections, especially in children or in an aggravated chronic inflammatory pathology, has been clearly demonstrated [29]. For these reasons, asking patients about exposure to active and passive tobacco smoke is crucial along with the age at onset of smoking (if relevant), the number of cigarettes smoked per day and the number of attempts to quit smoking. Information gained from these questions can provide useful information on nose functionality as reversibility of impaired nasal mucociliary clearance in smokers is observed from day 15 after stopping smoking [30]. This has also been demonstrated for COPD patients [31]. This topic is discussed further by Hurst and Huerta Garcia [32] elsewhere in this *ERS Monograph*.

Allergen sensitisation

A diagnosis of allergic rhinitis is based upon concordance between a typical history of allergic symptoms and diagnostic tests. A history of allergic symptoms and knowledge of the allergens responsible are crucial because their management can impact on the respiratory disease. Indeed, allergic rhinitis and sinusitis are associated with more severe asthmatic symptoms and can exacerbate asthma [33]. The impact of atopy on asthma is well recognised in the literature but, even though the literature is less abundant on COPD, it is also associated with an increased incidence and prevalence of nasal and respiratory symptoms [34].

In one study, allergic rhinitis was found in 59% of COPD patients [35]. Thus, interviews conducted with patients with nasal symptoms, whatever the associated respiratory disease, should focus on the timing of symptoms, seasonality, alleviating or aggravating factors (travel or occupational aggravation), contacts with animals and oral allergies. The severity of symptoms is classically assessed using bimodal evaluation, *i.e.* intermittent/persistent or mild/moderate-to-severe (table 3). For more details on interviews conducted with allergic patients, see Seidman *et al.* [36]. The interview with the patient is the cornerstone to orientate future prick tests and thus determine what kinds of allergens are responsible for the symptoms.

For cases where there is no evidence of allergies, the main causes of nonallergic rhinitis are detailed in table 4.

Occupational factors

Occupational nonallergic rhinitis is caused by the work environment through irritants and nonimmunological mechanisms. “Irritant-induced” occupational rhinitis classically refers to symptoms of rhinitis reported by subjects that are repeatedly exposed to irritants at work. Thus, a patient’s profession is of considerable importance, especially if the profession exposes them to dust and/or pollen, work with timber, professions where the “nose” is indispensable, or those that have a frequent risk of barotrauma. The link between occupational allergic rhinitis and occupational allergic asthma is well established [37].

Table 3. Severity of allergic rhinitis defined based on bimodal evaluation: intermittent/persistent or mild/moderate-to-severe

Intermittent/persistent		**Mild/moderate-to-severe**	
Intermittent	**Persistent**	**Mild**	**Moderate-to-severe**
<4 days per week or <4 consecutive weeks	>4 days per week or >4 consecutive weeks	All of the following: Normal sleep No impairment to daily activities No impairment to work and school Symptoms present but not troublesome	One or more of the following: Sleep disturbance Impairment to daily activities Impairment to work and school Troublesome symptoms

A detailed medical and occupational history remains a key step in the investigation and diagnosis of occupational rhinitis. The working conditions and a list of compounds utilised at the workplace should be collated. In cases of allergic rhinitis, this step is essential to determine prick tests to allergens and to discuss nasal challenge tests.

As observed in the “reactive airways dysfunction syndrome”, single or multiple exposures to very high concentrations of irritants can cause transient or persistent symptoms of rhinitis. The term “reactive upper airways dysfunction syndrome” has also been proposed [38].

Pollution

Possible exposure to atmospheric or industrial pollutants should be investigated. Various studies show that certain polluting agents reduce the threshold of sensitisation to allergens [39]. Other studies have demonstrated the deleterious effect of certain pollutants on mucociliary clearance and on the immune defence mechanisms of the respiratory mucous [40]. Indoor air pollution should also not be neglected. Exposure to tobacco smoke (as described earlier) is probably the main pollutant in many homes. Second-hand exposure to cigarette smoke is also associated with rhinitis, particularly in children and even without atopy [41]. Dampness and mould within homes can cause rhinitis and asthma [42, 43]. Questions regarding symptoms while at school are also important because children exposed

Table 4. Causes of chronic rhinitis

Allergic rhinitis
Infectious rhinitis (viral, bacterial, other)
Nonallergic rhinopathy: previously known as vasomotor rhinitis, irritant-induced rhinitis and idiopathic rhinitis
Nonallergic rhinitis with eosinophilia
Aspirin intolerance (aspirin triad)
Drug-induced rhinitis (*i.e.* rhinitis medicamentosa)
Hormonal-induced rhinitis (hypothyroidism, pregnancy)
Occupational rhinitis
Atrophic rhinitis
Senile rhinitis
Gustatory rhinitis (rhinorrhoea associated with eating)
Cerebral spinal fluid leak manifesting as rhinorrhoea
Structural conditions causing rhinitis (foreign body, nasal polyps, *etc.*)

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to poor air quality in classrooms have increase symptoms of rhinitis and asthma [44]. The association between air pollution and the nose in chronic respiratory disorders is discussed further by Charpin and Caillaud [45] elsewhere in this *ERS Monograph*.

Comorbidities

Reduced QoL and the economic burden of comorbidities caused by asthma and COPD are well known [46, 47]. The concept of comorbidities in CRS is still under discussion [48]. It can be complex to identify the pathophysiological mechanisms of "comorbidities" in rhinosinusitis and their implications for rhinosinusitis. Allergic rhinosinusitis has sometimes been identified as a comorbidity of asthma [49]. However, in this case, because there are always abnormalities in the nose of patients with asthma, it seems preferable to consider upper airway and lower airway dysfunctions as the same disease rather than comorbid conditions.

In a recent study, patients with a diagnosis of CRS had a higher pre-morbid prevalence of anxiety, headaches, gastro-oesophageal reflux disease (GERD), sleep apnoea and infections of the respiratory system, and the authors demonstrated that chronic illnesses often preceded a diagnosis of CRS [50]. Moreover, in asthma, the increased risk of obstructive sleep apnoea was associated with the concomitant presence of rhinitis [51]. Allergic and nonallergic rhinitis are also considered as risk factors for obstructive sleep apnoea [52]. Symptoms of gastro-oesophageal reflux should be also collected because nocturnal GERD is considered a risk factor for noninfectious rhinosinusitis [53]. Depression and anxiety should be investigated because they are prevalent in cases of CRS and respiratory disease [54].

Questionnaires

Several questionnaires have been developed to assess the severity and functional impacts of rhinitis and/or rhinosinusitis. These questionnaires help clinicians determine the severity of symptoms, the influence of rhinitis on a patient's QoL and the efficacy of a rhinitis treatment. In order to be useful in clinical practice, the questionnaires should not be time consuming, *i.e.* some questionnaire cannot be utilised by the clinician in daily practice. In the context of respiratory disease, Dixon *et al.* [55] developed a five-item questionnaire to screen for sino-nasal disease in asthma. This questionnaire has a sensitivity of 0.90 and a specificity of 0.94. Its usefulness in pulmonary clinics has been recently confirmed [56]. Other questionnaires have been established specifically for rhinitis and are detailed below. Scadding and Scadding [57] also discuss the use of QoL questionnaires in the broader context of "united airways" guidelines and clinical practice elsewhere in this *ERS Monograph*.

Visual analogue scale

The visual analogue scale (VAS) has the main advantage of being very easy to use and is nonspecific for a disease, but can be somewhat restrictive. A disease is classified according to the total severity VAS score (from 0 to 10): mild (0–3), moderate (3.1–7) or severe (7.1–10).

Allergic rhinitis

As described earlier, the severity of allergic rhinitis symptoms can be assessed using a number of tools (table 1). However, other questionnaires have been developed for this purpose, such as the Allergic Rhinitis Questionnaire [58] and the Rhinitis Symptom Utility Index [59]. To assess QoL, the Rhinoconjunctivitis QoL Questionnaire (RQLQ) is classically used; however, we think it preferable to use the mini-RQLQ with 14 questions.

Three main instruments are used to assess disease control in allergic rhinitis: the Control of Allergic Rhinitis and Asthma Test-10 with 10 items, the Rhinitis Control Assessment Test with six items, and the Allergic Rhinitis Control Test, which has similarities to the Asthma Control Test [60]. Whichever test is used, we consider it crucial to use a control test to assess if allergic rhinitis is controlled or not in order to standardise the follow-up.

Rhinosinusitis

In nonallergic rhinitis, the available instruments are the Rhinosinusitis Outcome Measurement-31, Rhinosinusitis Disability Index, Sino-Nasal Outcome Test (SNOT)-16 and -20 and RhinoQOL. SNOT-22 and RhinoQOL are the most commonly used questionnaires [61, 62].

Physical examination

Inspection

An examination always begins with inspection and palpation of the nasal pyramid, both face-on and in profile. The inspection should be done during both inspiration and expiration [9]. The existence of any deformation should be noted, *i.e.* a bump, angular features, lateral deviation (figure 2), deficiency or an exaggerated protuberance of the alar cartilage. A characteristic horizontal nasal fold may sometimes be found perpendicular to the nasal bridge, linked with repeated rubbing movements and nose blowing (also known as the classic “allergic salute”) [14]. Considering the importance of a granulomatosis with polyangiitis on the nose, the respiratory physician should be attentive to any potential erosion and perforation of the nasal septum or a “saddle-nose deformity” (collapsing of the bridge of the nose) [63].

The nasal valve should be examined with a simple retractor rather than using a speculum. This enables investigation of the morphology of the vestibule, the state of the septum, the appearance of the lower border of the upper lateral cartilages and the relief of the lower lateral cartilages. The clinical function tests for sniffing and voluntary nostril dilation can reveal any uni- or bilateral alar collapse and the absence of muscular contractions.

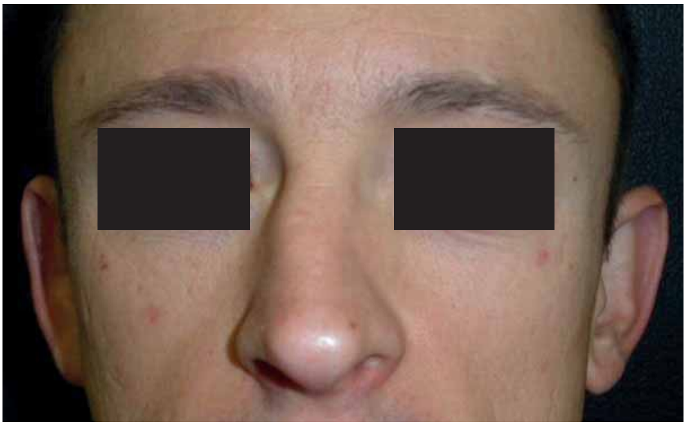


Figure 2. Inspection of the nose showing distortion.

An orbital examination is designed to detect scars resulting from a tear duct intervention, possible myosis or ptosis, enophthalmos or exophthalmos, or the presence of pus in the lacrimal canaliculi. Examination of the buccal cavity and teeth can indicate an occlusion (prognathism or retrognathism), a permanently open mouth or macroglossia. The remainder of the ENT examination is carried out systematically.

Palpation

In this section of the examination, the physician examines the skin, the underlying tissues, and the bony and cartilaginous parts for any irregularities, for any abnormal mobility and any pressure pain (sinusal points).

Anterior rhinoscopy

Anterior rhinoscopy remains the routine examination for nasal cavities and can be performed by any respiratory physician (figure 3a). It requires suitable lighting with a frontal lamp (Clar mirror) and a speculum or otoscope with a nasal adapter. It is carried out before and after nose blowing, and before and after vaporisation of a topical vasoconstrictor. A speculum is introduced into the nasal vestibule, first along the axis of the cavity floor, and then to its middle and upper portions. Compared with nasal endoscopy, this examination provides relatively limited data, but can confirm an architectural abnormality or septal deviation, a secretory abnormality (*e.g.* the presence of serous, mucous, purulent or crusty secretions), or a mucosal abnormality (*e.g.* hypertrophy or atrophy of the inferior turbinate mucosa). Abnormalities of the middle meatus are more difficult to visualise by anterior rhinoscopy, but polyps may sometimes be visible (figure 3b) and need to assessed in cases of asthma [64]. In asthma, polyps are usually not associated with atopy, and have a considerable impact on QoL and asthma control [65–67]. In purulent sinusitis, pus flow can be observed (figure 3c).

Posterior rhinoscopy

In posterior rhinoscopy, which is more difficult to carry out, different sized mirrors are used or, better still, a mirror that can be variably inclined by means of a lever on the handle. The mirror should be warmed to prevent it misting over. It is then introduced behind and below the soft palate, while downward pressure is applied to the tongue with a spatula. Even if a local anaesthetic is administered, the nausea reflex or the size of the velum may prevent observation of the cavum and the posterior portion of the nasal cavity. These reasons explain the limitations of posterior rhinoscopy and why it is rarely performed in practice. Nasal endoscopy is preferred.

Nasal endoscopy

The current use of flexible or rigid optical instruments permits a much more detailed examination of the different turbinates and the meatus up to the sinus ostia [68, 69]. Nowadays, the use of flexible instruments is more widespread and they are commonly utilised by laryngologists. In general, especially when a thin (2.7 mm) endoscope is used, local anaesthesia is not necessary.

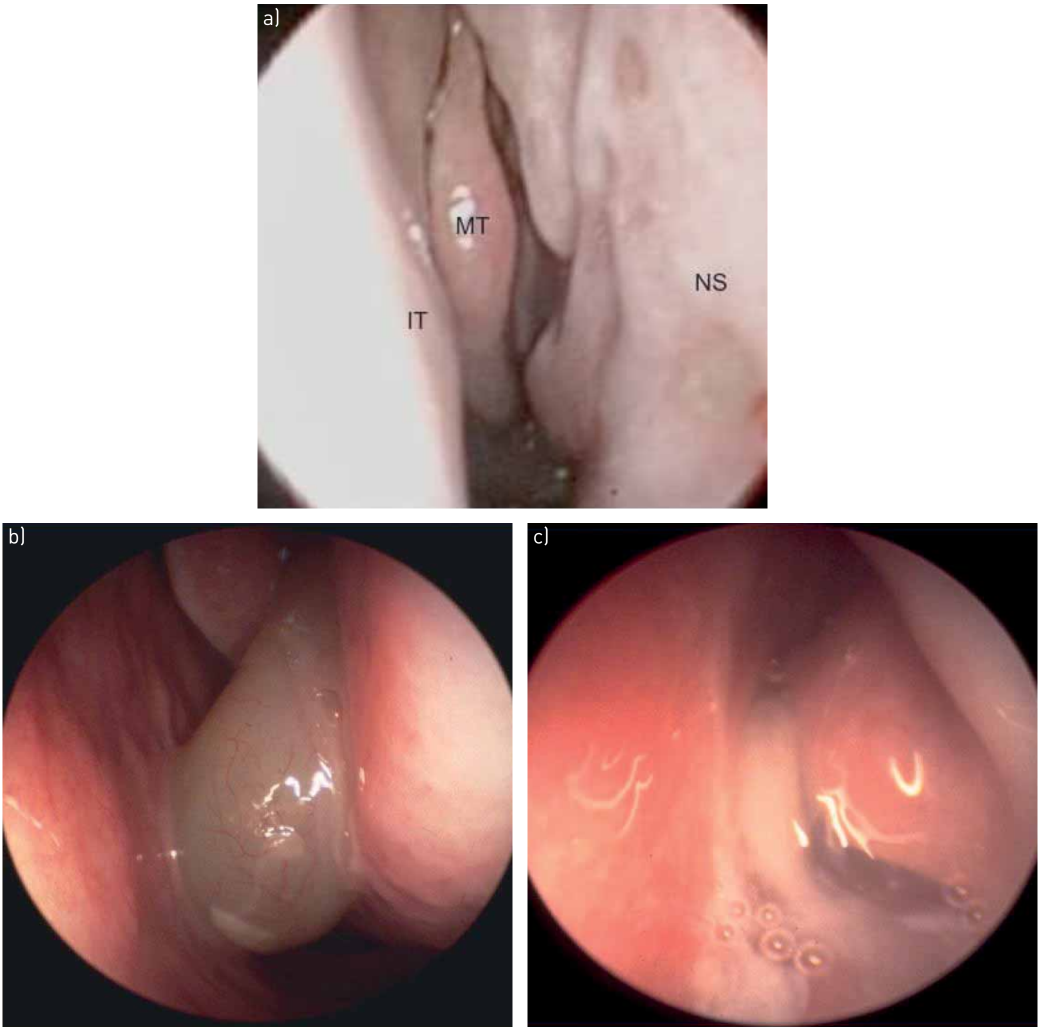


Figure 3. a) Normal anterior rhinoscopy (right side). IT: inferior turbinate; MT: middle turbinate; NS: nasal septum. b) Nasal polyposis observed during an anterior rhinoscopy (left side). c) Pus flow observed during an anterior rhinoscopy (left side).

Nasal endoscopy is carried out before and after spraying with a vasoconstrictive and anaesthetic solution. Both nasal cavities and the cavum can then be thoroughly explored from front to back, and then from back to front. Anterior median and posterior endoscopy is then performed. Specific regions can be more closely examined depending on the context: always the middle meatus, but sometimes the inferior meatus and olfactory cleft. Endoscopy also permits palpation of certain structures, particularly the inferior turbinate, so that hypertrophy of the inferior turbinate mucosa, with its classic "eiderdown" appearance, can be distinguished from osseous hypertrophy of the inferior turbinate, which feels hard on palpation [70, 71].

Compared with anterior and posterior rhinoscopy, nasal endoscopy is the best clinical tool to detect polyps. As described previously, a diagnosis of polyps is fundamental in patients with asthma due to its impact on QoL and asthma control. Even if the link between chronic rhinitis/polyps and COPD still remains ambiguous, both cross-sectional and clinical studies suggest an association between smoking and nasal disease [72, 73]. Sino-nasal signs that are potentially observable in nasal endoscopy should not be neglected in this subpopulation.

During endoscopy, nasal secretions can be directly sampled for cytological and/or bacteriological analyses (nasal smear or pus sample). The presence of allergic mucin and polyps in a nasal endoscopy suggests a diagnosis of allergic fungal rhinosinusitis. This entity, similar to allergic bronchopulmonary asthma, must be identified by chest physicians because, in one study, 14.2% of patients suffered from asthma [74].

Nasal endoscopy thus permits a differential diagnosis of congenital, tumoral, architectural, inflammatory and infectious pathologies.

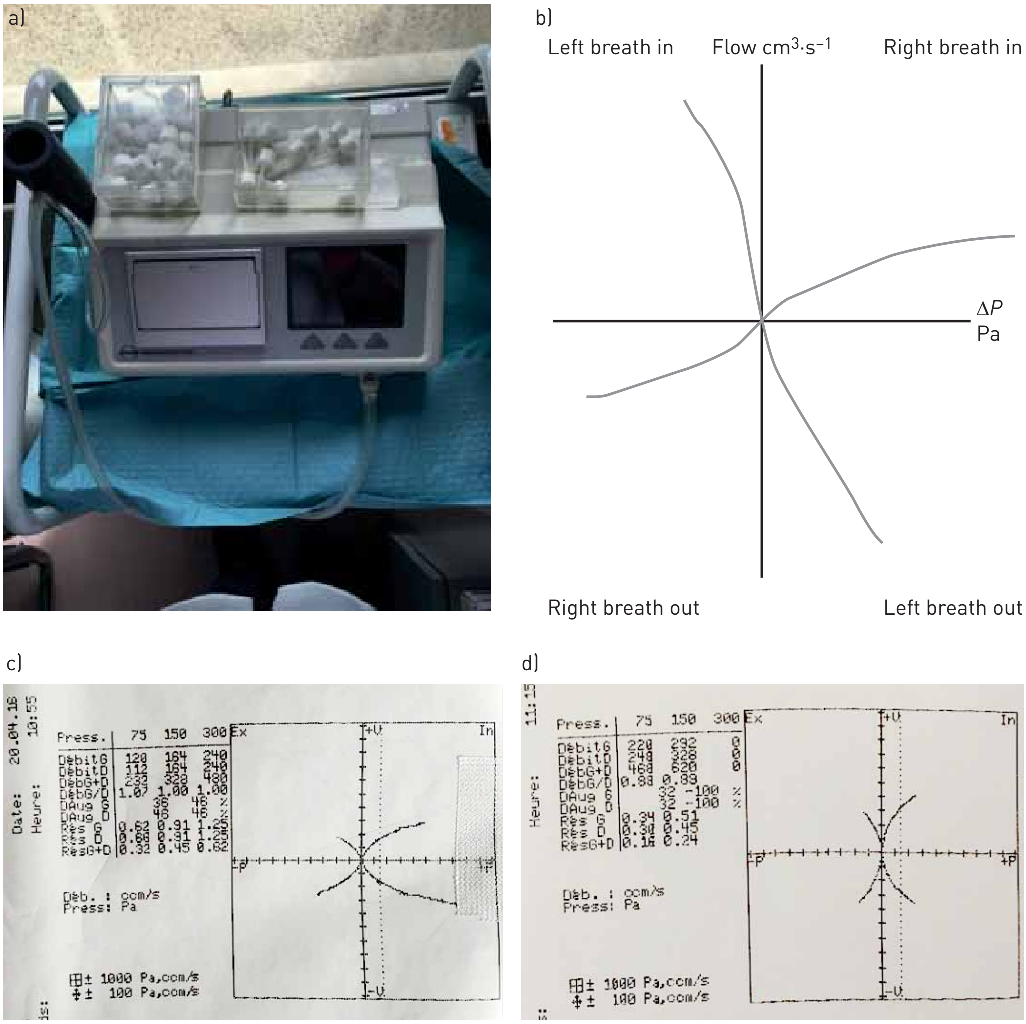
Rhinomanometry

This set of techniques allows simultaneous measurement of variations in flow and pressure of the air current as it passes through the nasal cavities (figure 4). The data are used to calculate nasal resistance as based on Poiseuille's law. Airflow and nostril pressure are measured inside a mask covering the nose and mouth [75]. Choanal pressure is measured in the contro-lateral nostril during active anterior rhinomanometry and in the buccal cavity during active posterior rhinomanometry. Due to obstruction of one of the nostrils, anterior rhinomanometry cannot be used to study both nasal cavities simultaneously. Active anterior rhinomanometry is a simple and rapid procedure, it is reproducible, and it is feasible in all patients, including children. Active posterior rhinomanometry, in contrast, is difficult to carry out in certain patients due to the introduction of a buccal probe. However, it has the advantage of measuring overall resistance and provides a better picture of the nasal valve by eliminating the nostril rims. Total nasal resistance is normally $<0.3\ \mathrm{P{\cdot}mL^{-1}{\cdot}s^{-1}}$ and normal unilateral resistance is $<0.6\ \mathrm{P{\cdot}mL^{-1}{\cdot}s^{-1}}$.

Rhinomanometry is carried out after blowing the nose in a quiet, airy room and not in sunlight. The exploration is complete when the resulting values are normal. With cases of supine nasal obstruction, a second measurement is made after lying the subject of his/her back for 30 min. When nasal resistances are high, different manoeuvres are performed to determine which anatomical structures are involved. Cottle's test (opening of the naso-genial line to increase valve angle) and Bachmann's test (insertion of a swab into the top of the nasal valve) are considered positive if the resistances return to normal when they are performed. A positive value implies that the valve is involved. When the vasoconstrictor test returns the nasal resistances back to normal, this indicates that the nasal obstruction is caused by turbinate hypertrophy [76].

Rhinomanometry cannot be used to precisely quantify nasal obstruction [77]. Indeed, there is no correlation between the magnitude of the increase in nasal resistance and the severity of the obstruction felt by the patient.

Studies on rhinomanometry have provided useful information on nasal resistance and emphasise that nasal obstruction should not be neglected. Indeed, patients with a negative decongestion test show significantly increased grades of bronchial hyperreactivity [78]. COPD patients have higher nasal resistances compared with controls [79].



c)

Date: 20.04.18
Heure: 10:55

Press.	75	150	300	
DébitG	120	164	240	
DébitD	112	164	240	
DébG+D	232	328	480	
DébG/D	1.07	1.00	1.00	
DAug G		36	46	%
DAug D		40	46	%
Rés G	0.62	0.91	1.25	
Rés D	0.66	0.91	1.25	
RésG+D	0.32	0.45	0.62	

Déb. : ccm/s
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田± 1000 Pa,ccm/s
‡± 100 Pa,ccm/s

d)

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Press.	75	150	300	
DébitG	220	292	0	
DébitD	248	328	0	
DébG+D	468	620	0	
DébG/D	0.88	0.88		
DAug G		32	-100	%
DAug D		32	-100	%
Rés G	0.34	0.51		
Rés D	0.30	0.45		
RésG+D	0.16	0.24		

Déb. : ccm/s
Press: Pa

田± 1000 Pa,ccm/s
‡± 100 Pa,ccm/s

Figure 4. Technical aspects of rhinomanometry. a) A rhinomanometer. b) Example of a rhinomanometry result. c) Print-out of a pre-test anterior rhinomanometry curve before a vasoconstrictor test. d) Print-out of a post-test curve showing normalisation of the airflow and nasal pressure after a vasoconstrictor test.

Rhinomanometry is of particular benefit for nasal challenges used to measure the specific reactivity of the nasal mucosa to different allergens [80], and has progressed and standardised this approach. Nasal challenges consist of measuring variations in nasal resistance before and after introducing a suspected allergen. The allergen may be introduced in different ways (direct application to the nasal mucosa, nasal spray of the allergen solution, aerosol, *etc.*) [81].

A very strict protocol is required to prevent contamination of the bronchi with the allergenic solutions. Positive criteria are doubling of nasal resistance and dose-dependent clinical effects. Local treatments and antihistamines should be stopped for at least 48 h before the test and no acute infection should be present. However, these tests are time consuming, so only a single allergen can be tested per session. They must therefore be reserved for complex clinical situations in which the clinical history and skin tests do not clearly identify the allergen(s) involved. These tests are therefore used, for example, in the

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cases of polysensitisation to determine the respective roles of different allergens or, inversely, when there is a strong clinical presumption of sensitisation to an allergen that cannot be confirmed by the usual methods. This latter situation is particularly frequent in occupational allergies [37]. A nasal challenge with aspirin can be helpful in diagnosing aspirin-induced rhinitis [82, 83].

Peak nasal inspiratory flow

On the basis of peak expiratory flow, which is widely used to monitor airway obstruction in asthma, peak nasal flow has been developed to assess nasal patency [84]. Peak nasal inspiratory flow (PNIF) has more advantages than peak nasal expiratory flow (PNEF). PNIF is more hygienic and seems to correlate better with nasal resistance than PNEF. PNIF is a cheap, fast and portable technique that is simpler to use than rhinomanometry [80]. It measures nasal flow and gives a direct measure of nasal obstruction. The technique consists of a face mask applied over the nose with the mouth closed. Three satisfactory maximal inspirations are usually obtained and the highest result of the three is taken as the PNIF [80, 85]. In clinical practice, PNIF can be used to evaluate treatment in allergic rhinitis in adults and children, to test nasal provocation associated with nasal hyperreactivity (allergens, aspirin, *etc.*), and to evaluate environmental effects in occupational rhinitis [86–88].

Acoustic rhinometry

This technique is based on acoustic scanning, and it supplies information on nasal patency and provides an objective geometric study of the nasal cavities [89]. Computerised analysis of the reflection of sound waves in the nasal cavities is used to deduce a "section area" for each location over time. Knowing the speed of sound, the distance to the site of the location within the nasal cavity can be determined. Jackson *et al.* [90] in 1977 and then Hilberg *et al.* [91] in 1989 described the principle whereby a pressure wave, emitted by a generator, is directed into the nasal cavity through a tube of constant calibre. A microphone placed at the end records the reflection of the wave after its passage through the nasal cavity, and this signal is then amplified, filtered and analysed by appropriate software.

Acoustic rhinometry enables an obstacle within the nose to be quantified and situated on a curve with three undulations in the form of negative waves: the first peak is fixed and corresponds to the end of the nasal tube, and is situated ~0.5 cm beyond the nostril orifice; the second peak is situated ~2 cm from the nostril orifice and corresponds to the valve region and the head of the inferior turbinate; the third peak is located ~6 cm from the nostril orifice and corresponds to the tail of the inferior turbinate.

In patients with turbinate hypertrophy, the smallest section area is situated at the head of the inferior turbinate [92]. Large variations are apparent, especially beyond the first 3 cm into the nasal cavity where the method remains imperfect. The advantages of this technique are its rapidity, reproducibility, noninvasive character and the minimal cooperation required by the patient [89, 93, 94]. Nevertheless this method still requires validation [94] and numerous technical problems remain unresolved [80]. The concept of a "united airways" is crucial, and a strong and consistent association between upper and lower airway patency has been found in asthma patients [95]. These measurements are probably most useful to assess nasal patency before and during a challenge (*e.g.* allergen, aspirin, methacholine, *etc.*).

Acoustic rhinometry is less reliable than endoscopy to estimate the degree of subjective nasal symptoms [96].

Exploration of mucociliary function

Examination of mucociliary function is not carried out in daily clinical practice. However it should be systematically used in cases of chronic purulent or bilateral recurrent sino-nasal infection. Several methods of exploration can be used. The best clinical test for mucociliary clearance is saccharin transit time [97]. This consists of placing saccharin powder on the inferior turbinate. The time needed by the patient to taste the saccharin is usually <20 min.

The techniques used to study ciliary beat rate and electron microscopy of the ciliary structure are more specific [98]. Investigation of the ciliary structure is lengthy and costly, and is only undertaken in patients selected on the basis of a ciliary beat study [99]. Indeed, it is unlikely that an abnormality is found if the beat is normal. However, these methods are useful to diagnose primary or secondary ciliary dyskinesia and Young's syndrome (which combines chronic rhinosinusobronchitis and obstructive azoospermia caused by poor mucus viscosity).

Cellular exploration: nasal cytology

This can involve taking a smear or nasal brushing. The nasal smear is obtained under optical control, with a Dacron swab inserted up as far as the middle turbinate. This swab is wiped over the outer surface of the middle turbinate in the nonanaesthetised nasal cavity, taking care not to cause bleeding. It is then smeared, but not squashed, on to a glass slide and fixed in air or with a cytological fixative. The different epithelial cells and percentages of each type of leukocyte are measured semiquantitatively by May–Grünwald–Giemsa staining [100]. The smear must be performed in the absence of any superinfection and at 15–21 days after any steroid treatment.

The normal nasal mucosa does not contain polynuclear neutrophils or eosinophils. Free cells exist in the nasal mucus and most of these are polynuclear neutrophils. A nasal cytology examination is appropriate in the context of a chronic disease of the nasal mucosa [101]. In allergic patients undergoing exposure to allergens, the mucosal and secretory eosinophils are dominant [102]. However, infiltration of polynuclear eosinophils is not synonymous with an allergy. Nonallergic rhinitis with eosinophilic syndrome (NARES) is an inflammatory rhinitis that is characterised by secretory eosinophilia [103]. According to the nasal cytology, the "cellular" forms of rhinitis can be subdivided into nonallergic rhinitis with neutrophils (NARNE), NARES, nonallergic rhinitis with mast cells (NARMA) and nonallergic rhinitis with eosinophils and mast cells (NARESMA) [100]. NARES, NARMA and NARESMA often co-occur with nasal polyposis and/or asthma, and/or sensitivity to aspirin. Chest physicians should be aware of these entities.

This examination can only provide a valid interpretation if strict sampling and criteria are respected [100]. It therefore requires experience on the part of the operator and the laboratory. In practice, the results are mainly used to eliminate NARES in cases of chronic rhinitis. The nasal cytology in the context of polyposis is also very relative. In fact, neither a diagnosis or treatment of polyposis is dependent on the cytology.

Olfactory exploration

Exploring the sense of smell is poorly accessible in daily clinical practice, although impaired smell or taste can have a substantial impact on QoL and is not uncommon even in allergic rhinitis [104]. The devices most often proposed to patients to identify different aromas are rigid "sniff bottles", perfume testers or microcapsules that release odorant molecules when scratched. The olfactory test developed by the University of Pennsylvania, and commercialised as the "Smell Identification Test" ("UPSIT"), permits qualitative identification of different smells. It consists of a four-page booklet, each containing 10 microencapsulated "smell" molecules. The patient chooses between four possible answers for each stimulus. The score is calculated by comparing the number of correctly identified aromas out of a total of 40 different aromas. Another validated olfactory tests is the Sniffin' Sticks test [105, 106].

Conclusions

In daily practice, examination of the nose mainly relies on meticulous questioning of the patient followed by a complete clinical examination of the upper respiratory tract. Any practitioner can perform an anterior rhinoscopy using a frontal lamp and a speculum or an otoscope with a nasal adapter before and after vaporisation of a topical vasoconstrictor. This first step may be followed, if necessary, by flexible or rigid endoscopy, but this require specialised instruments and medical experience.

PNIF is an easy-to-use tool to evaluate nasal resistance. Other examinations, such as rhinomanometry, nasal cytology, mucociliary function or olfactory explorations, are less frequently conducted, and depend on data obtained after questioning the patient and the initial examination. Clinicians involved in respiratory diseases should be aware that investigating the nose in the management of the "united airways" can be a highly valuable approach.

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Chapter 3

Imaging the nose and sinuses in respiratory disorders

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Present-day imaging of the nose and paranasal sinuses is mainly done by slice-based imaging modalities such as CT, cone beam CT and MRI, which have much higher performance than conventional plain films. Although CT has the highest spatial resolution, MRI provides the best contrast analysis and tissue characterisation. Cone beam imaging has the advantage of imaging dental structures and paranasal sinuses together with a lower irradiation burden than CT. Here, we describe the imaging modalities, normal results and variants, and imaging features of inflammatory diseases of the nose and sinuses. The particular aspects of imaging the paranasal sinuses in CF are addressed.

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Imaging of the nose and the sinuses has evolved with the development of imaging techniques. Plain radiographs have been replaced by slice-based imaging modalities such as high-resolution CT (HRCT), cone beam CT (CBCT) and MRI. Plain radiography is a two-dimensional technique that does not allow correct evaluation of the ostiomeatal complex, sphenoidal cells and ethmoidal cells owing to superimposition of anatomical structures. Conversely, CT and MRI are three-dimensional imaging modalities that allow us to perform multiplanar reconstructions (MPRs) in the frontal and sagittal planes starting from a native axial volumetric acquisition. For instance, MPR images can prove useful in the surgical management of patients before endo-nasal intervention. CT is a powerful technique to assess bone structures. Conversely, MRI benefits from contrast resolution to better characterise the inflammatory processes in soft tissue or to evaluate the loco-regional extension of a sino-nasal tumour. Clinical data are fundamental to adapt imaging examinations to specific disease conditions. Interpretation of imaging requires knowledge of the normal anatomy and possible typical variations. Finally, knowledge of sino-nasal physiology and mucociliary clearance is necessary for appropriate management of inflammatory upper airways diseases.

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Anatomy of the nose and sinus cavities

Nasal cavity

The nasal cavity is divided by a vertical partition into the right and left nasal passageways. This partition is called the nasal septum, and comprises a cartilaginous part towards the front of the nose and a bony part towards the back. At the front, the left and right sides of the nasal cavities form the two nares ("nostrils"), which are separated by the quadrangular cartilage. Towards the back, the bony septum is composed of four elements: the perpendicular plate of the ethmoid bone, the vomer, the nasal crest of the maxilla and palatine bones. The nasal passageways end in the right and left choanae, and open into a chamber called the nasopharynx. The nasopharynx contains lymphoid tissue called the adenoids (or pharyngeal tonsils) towards the midline. The Eustachian tubes open into each side, and connect the nasopharynx to the right and left middle ears.

The lateral walls of the nasal cavity are composed of bony side walls. Three finger-shaped structures called the turbinates (or nasal conchae) are attached to these sidewalls. The turbinates are made up of a bony core and an outer soft tissue. They help to increase the surface area of the mucosa and also to smooth the nasal airflow towards the lung (figure 1a). A hole termed a meatus, whose name is determined according to the turbinate above (*i.e.* superior, middle or inferior), opens between the turbinates. The naso-lacrimal duct drains the tears beneath the inferior turbinate into the inferior meatus.

Sphenoid sinuses

Embedded into the sphenoid bone, the sphenoid sinuses are divided by a vertical wall, and present with a variable degree of size and shape (figure 1b). They are rarely symmetrical. In some cases, they may extend up to the pterygoid processes and the greater wings (alisphenoids), and may invade the basilar part of the occipital bone. The sphenoid sinus and the posterior ethmoid sinus cells drain into an area between the nasal septum and the superior turbinate called the spheno-ethmoid recess, directly above the choanae. These apertures are located on the anterior walls of the sinuses.

Ethmoidal sinuses

Ethmoidal air cells of the ethmoid bone are variable both in size and number in the lateral mass of each ethmoid bone (figure 1b). They consist of thin-walled cavities located in the

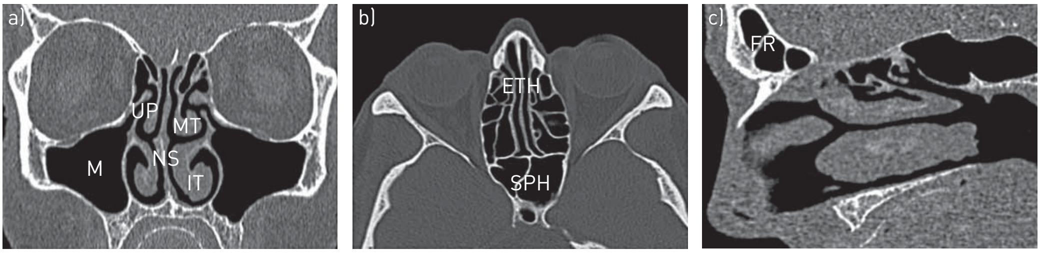

Figure 1. High-resolution CT of the nose and paranasal sinuses with multiplanar reconstructions in the a) frontal, b) axial oblique and c) sagittal planes, showing features of normal anatomy. M: maxillary sinus; UP: uncinate process; NS: nasal septum; MT: middle turbinate; IT: inferior turbinate; ETH: ethmoidal sinus; SPH: sphenoidal sinus; FR: frontal sinus.

ethmoidal labyrinth, at the upper part of the nasal cavities and the orbit. There are three groups of cavities. The anterior ethmoidal sinus drains into the middle meatus by way of the infundibulum. The medial limit of the infundibulum is the uncinate process and the lateral limit is the inferior wall of the orbit. The middle ethmoidal sinus drains into the middle meatus. The posterior ethmoidal sinus drains into the superior meatus.

Frontal sinuses

These cavities are located in the anterior part of the frontal bone (figure 1c). They present a pyramidal shape, with the base being oriented to the top of the cavity. The extent of skeletal pneumaticity is variable. The septum between them frequently deviates from the middle line. Each of the right and left cavities opens into the anterior part of the middle nasal meatus through the fronto-nasal duct which runs through the anterior part of the labyrinth of the ethmoid. These tubes end in the hiatus semilunaris in the middle meatus.

Maxillary sinuses

These cavities are located in the central part of the maxillary bones and are frequently asymmetrical. They represent the largest air sinus in the body (figure 1a). The shape is pyramidal, with a nasal wall or base, a posterior wall, a floor and a roof formed by the floor of the orbit. This paranasal sinus drains into the middle meatus of the nose. There are three recesses: a zygomatic recess laterally, an infraorbital recess pointed superiorly and the alveolar process of the maxilla pointed inferiorly. The sinus is lined with a membrane called the Schnederian membrane, which is histologically a mucoperiostum with cilia that beat towards the ostia.

Skeletal pneumaticity

Pneumaticity (*i.e.* the development of air spaces) of the paranasal sinuses is progressive in children. From an embryological point of view, all sinuses are derived from the ethmoidal cells. The ethmoid sinus is the sole aerated structure at birth. Pneumaticity of the maxillary sinus occurs at age 4 years, the sphenoidal sinus at age 6 years and the frontal sinus at age 12 years. Skeletal pneumaticity continues until age 18 years.

Imaging techniques

High-resolution computed tomography

HRCT allows thin-section image acquisition in the axial plane, parallel to the bone palate [1]. The patient is placed in a supine or prone position associated with hyperextension of the neck. As a result of the isotropic resolution of the volume acquired, MPRs can be performed using a single CT examination, at least in the frontal and sagittal planes. Millimetre or submillimetre slices without slice intervals are nowadays performed. Imaging reconstruction must be completed using both bone and soft tissue filters. There is usually no need for contrast agent injection, except in the clinical context of a sinus tumour. The nasal cavity and paranasal sinuses appear entirely aerated under normal conditions. The normal thickness of the mucosa is <1 mm at the level of the paranasal sinuses and <2 mm at the level of the nasal cavity. However, there are physiological variations in the mucosal thickness between the right and left sides according to the vascular nasal cycle. Radiation

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shielding of the sensitive tissues of the gonads, eyes, breast and thyroid can be used, especially in children. Three main points can be considered for analysis: the description of the lesions, the description of extent of the lesions (permeability of ostia, integrity of bone walls, perisinusal fat, *etc.*) and the presence of anatomical variants (at risk for surgery, at risk for sinusitis or responsible for symptoms).

Cone beam computed tomography

CBCT (also referred to as C-arm CT, cone beam volume CT or flat panel CT) is an advancement in CT imaging that has emerged as a low-dose cross-sectional technique for visualising bony structures of the maxilla for dental structures and sinuses [2]. It is a medical imaging technique where the X-rays diverge, forming a cone. Isotropic spatial resolution and relatively low dose requirements have made it attractive for office-based and intraoperative scanning of the paranasal sinuses. The use of CBCT has been advocated in the context of intraoperative and perioperative structural evaluations, enabling assessment of parasinusal anatomy, surgical outcomes and stent placement. However, there is no current evidence supporting CBCT use in general diagnostic sinus imaging owing to a lack of soft tissue contrast resolution.

Magnetic resonance imaging

MRI is useful in assessing sinus tumours and intracranial complications of both infectious and tumoural diseases [1]. T1- and T2-weighted sequencing are performed, and there is great variability of signal intensity resulting from differing protein concentrations. Fat-suppressed T1-weighted post-contrast sequences are useful for the evaluation of the extent of extra-sinusal infection/inflammation or the evaluation of sino-nasal masses. Fat-suppressed T2-weighted sequences are useful for the evaluation of disease extent and extra-sinusal involvement. The combination of T1- and T2-weighted contrast together with contrast agent injection can improve detection and characterisation of lesions, *e.g.* to discriminate inflammatory mucosal thickening from pus [3], and diffusion MRI may be useful for discriminating malignant tumours [4]. MRI has long been considered inferior to CT in assessing sinus morphology because of susceptible artefacts near bone structures. Nevertheless, the recent advent of MRI with ultra-short echo time has made it feasible to image bone structures with a fine resolution comparable to that of CT [5]. The absence of exposure to ionising radiation may be considered an advantage in young people with iterative imaging examinations, such as for CF.

Angiography

The role of angiography to explore the nose and paranasal sinuses is limited to cases of epistaxis resistant to conventional treatment prior to embolisation.

Anatomical variants at risk for surgery, sinusitis or dural puncture

Knowledge of the anatomical variants of paranasal sinus anatomy is essential for understanding imaging patterns of inflammatory processes, and is essential for guiding functional endoscopy and surgery.

Variations of pneumaticity

Overpneumatisation

The term hypersinus (or mega sinus) refers to an overexpansion of air within a sinus, without wall expansion. Pneumosinus dilatans refers to an expansion of both the lumen and wall of the sinus, but without wall thinning. Pneumocele (or pneumatocele) refers to a sinus with normal pneumaticity and normal epithelium, but thinning of the sinus layers (either diffuse or focal). The frontal sinus is the paranasal cavity that most frequently presents this variation (63% of cases), followed by the maxillary sinus (15%), sphenoidal sinus (12%) and ethmoidal sinus (10%). Overpneumatisation may be acquired after repeated hyperpressure events such as nose blowing, Valsalva manoeuvre and cough. It may be focal or diffuse and may expose a vascular or neural path, and is a source of headache, neural compression, dural puncture and brain incarceration.

Hypopneumatisation

This variation is relatively frequent, up to 5% with regard to the frontal sinus. It may increase the difficulty of access to deep structures during surgery (*e.g.* to the pituitary gland).

Variations of the nasal cavity

Septal deviation

This is a common variant found in up to 48% of patients (figure 2). It may be associated with a bony angulation that can prevent the completion of endoscopy.

Uncinate process

A superior attachment of the uncinate process is sometimes located on the lateral wall of the orbit and may increase the risk of ocular traumatism during surgery. The same

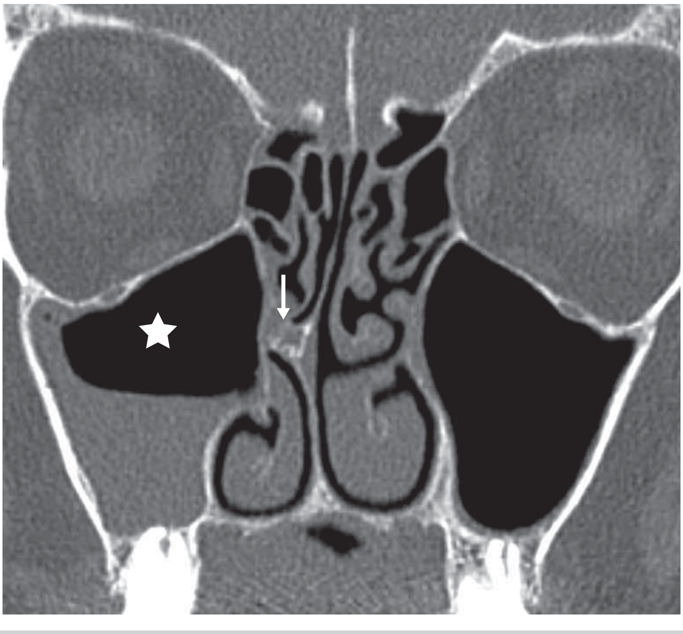

Figure 2. Coronal high-resolution CT reconstruction of the paranasal sinuses. White arrow indicates a right-sided septal deviation with bony angulation and narrowing of the middle meatus. White star indicates an air-fluid level related to an acute sinusitis of the right maxillary sinus.

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attachment may occur on the middle turbinate or the ethmoid and can increase the risk for dural puncture.

Lateral deviation with retraction can be associated with maxillary sinus hypoplasia. It increases the risk for orbital traumatism.

Overpneumatisation is rare and could be related to a displacement of the anterior ethmoidal cells.

Superior meatus narrowing

This variation is at higher risk of sinusitis and may be secondary to an overpneumatisation of the vomer.

Variation of the sphenoidal sinus

Mega sphenoidal sinus

Aberrant pneumatisation of the sphenoid can occur up to the dorsum sellae and stops near the spheno-occipital synchondrosis. There is a risk for vascular traumatism with an intracavernous carotid (figure 3).

Intrasinusal optic nerve procidence and anterior clinoid pneumatisation

Both variants increase the risk of neural damage during surgery and inflammation during sinusitis.

Variation of the ethmoidal sinus

Agger nasi cells

Pneumatisation of the anterior ethmoidal cells (figure 4a), which may interfere with naso-frontal drainage.

Onodi cells

Posterior ethmoidal cells are called Onodi cells (figure 4b). Some risk of infection exists during surgery as a result of their contact with the optical nerve pathway.

Dehiscence of the lamina papyracea

This variant usually occurs near the insertion of the middle turbinate and may be at risk for orbital trauma (figure 4c).

Asymmetry of the ethmoid roof

A lower position of the fovea ethmoidalis exists in 3.5% of cases. A difference between the right and left sides of >2 mm should be reported (figure 4d). This anomaly is prone to increase the risk of ethmoidal puncture. Such an anomaly is more frequent in the anterior part of the roof and on the right side. Associated thinning of the roof increases the risk of vulnerability during surgery.

Variation of the frontal sinus

Identifying the obliquity of the frontal sinus drainage used to be difficult without MPR reconstructions. The use of sagittal reconstructions now allows optimal visualisation of the geometry to plan surgery.

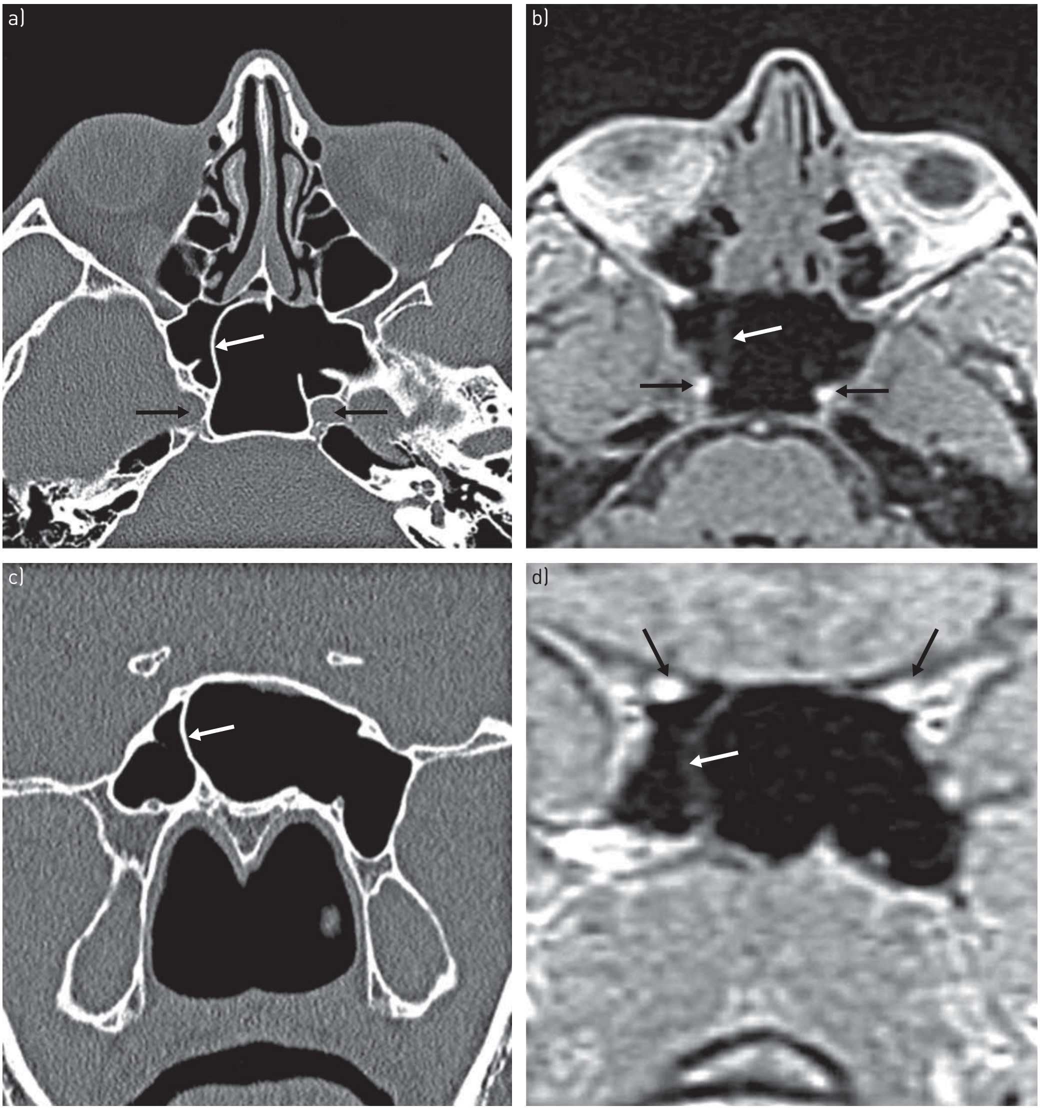

Figure 3. a, b) Axial and c, d) coronal views of the sphenoidal sinus using a, c) high-resolution CT and b, d) T1-weighted MRI with ultra-short echo time. There is an overpneumatisation of the sphenoidal sinus. White arrows show a sphenoid sinus septation visible with all imaging modalities, although with better delineation using CT. a, b) Black arrows indicate an intrasinusal procidence of the intracranial carotids. d) Black arrows indicate an intrasinusal procidence of the optic nerves, only visible using MRI.

Variation of the maxillary sinus

Hypoplasia of the maxillary sinus

The maxillary sinus develops until age 15 years. An absence of development may be idiopathic, either alone or in combination with a malformation of the first bronchial arch. It may also be secondary to surgery or trauma. The frequency has been reported to be ~8.9% in the general population. It is bilateral in 75% of cases. The diagnosis may remain occult until adulthood (figure 5).

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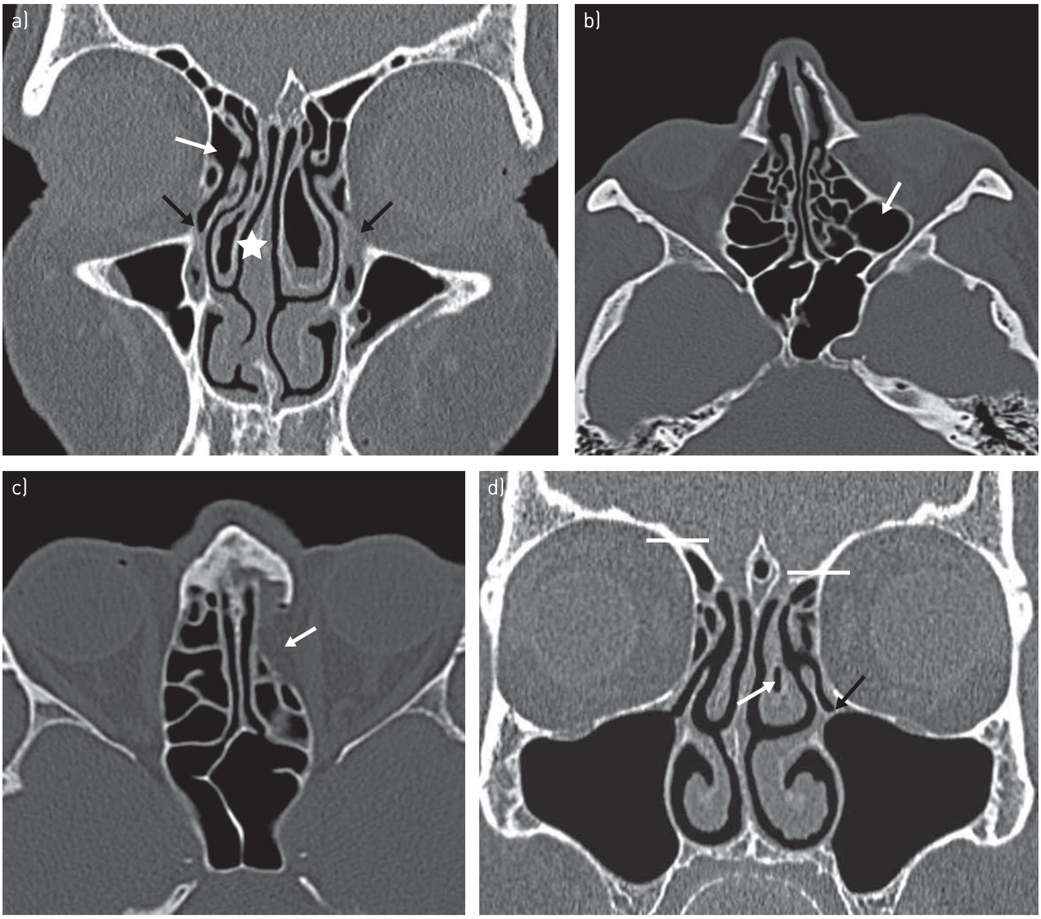

Figure 4. a) Coronal high-resolution CT reconstruction of the paranasal sinuses. White arrow indicates an enlarged agger nasi cell. Black arrows indicate narrowing of the right naso-lacrimal duct compared with the left naso-lacrimal duct. White star shows a paradoxical curvature of the right middle turbinate. There is also a concha bullosa of both turbinates. b) Axial high-resolution CT of the ethmoidal sinus. White arrow indicates an enlarged Onodi cell. c) Axial high-resolution CT of the ethmoidal sinus. White arrow indicates a dehiscence of the medial orbital wall. d) Coronal high-resolution CT reconstruction of the paranasal sinuses. White arrow shows a concha bullosa. There is a lateral displacement of the uncinate process, responsible for narrowing of the infundibulum of the maxillary sinus (black arrow). Note a pneumatisation of the crista galli. Horizontal bars indicate an asymmetry in the ethmoidal roof of >2 mm.

Sinus septation

Additional partition of the sinus cavity is frequently observed, especially in the maxillary sinus with additional ostia (40%). These additional anatomical components may be prone to false-positive meatus and cavities during surgery, leading to incomplete or inadequate treatment.

Narrowing of the infundibulum

This variation is at risk for sinusitis and may occur under the presence of several anatomical variations.

Haller cell

This is a pneumatised ethmoidal cell which occasionally develops along the internal orbital wall (figure 6). The frequency ranges from 7% to 45% of cases.

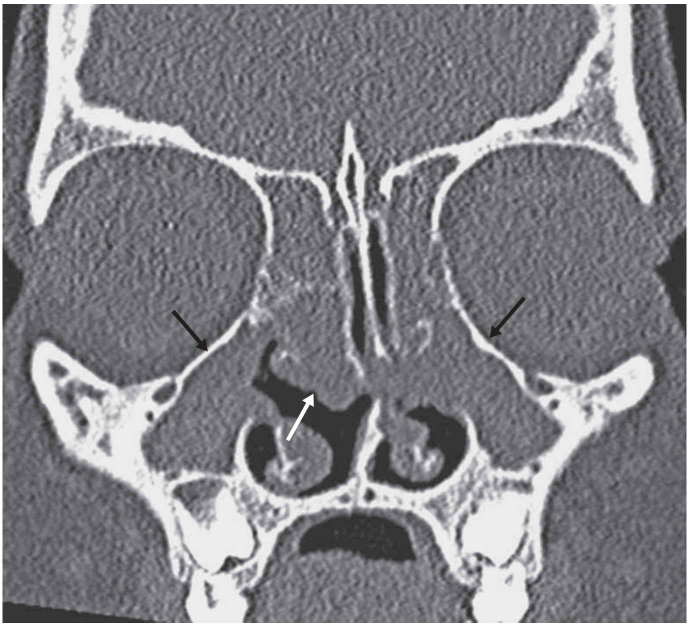

Figure 5. Coronal high-resolution CT reconstruction of the paranasal sinuses in a young patient with asthma. There is bilateral hypoplasia of the maxillary sinuses and procidence of the orbital floors (black arrows). White arrow indicates intranasal polyp development starting from the middle turbinate.

External deviation of the uncinate process

This variation is frequently associated with a hypoplastic maxillary sinus (figure 4d).

Concha bullosa

This variation is related to an overpneumatisation of the middle turbinate (figure 4d). This is the most common cavitation occurring in turbinates (30%) and secondary to a migration of anterior ethmoidal cells (55%) or posterior ethmoidal cells (45%). There is an ostium that opens in the naso-frontal recess in 80% of cases.

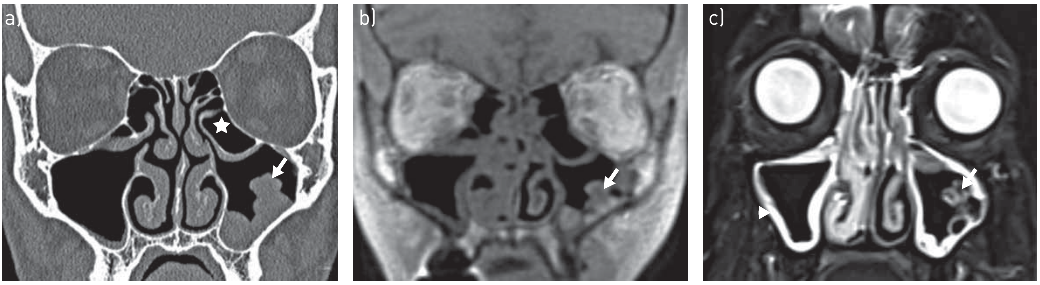

Figure 6. Mycetoma. Coronal view of the paranasal sinuses using a) high-resolution CT, b) T1-weighted MRI sequence using ultra-short echo time and c) T2-weighted MRI sequence. a) White star indicates a Haller cell. White arrowhead on c) indicates inflammatory thickening of the mucosa with hyperintense T2 water-like contrast. White arrows show a fungal polyp (mycetoma) that appears with b) T1 isointensity and c) marked T2 hypointensity. Note the difference of signal between the fungal polyp and inflamed mucosa on MRI, whereas attenuation of both is similar on unenhanced CT.

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Paradoxical curvature of the middle turbinate
The curvature is reversed compared with a normal inferior concavity (figure 4a). The frequency is 11–34%.

Imaging of sino-nasal diseases

This section will focus on imaging features of inflammatory diseases and conditions related to respiratory diseases. The description of sino-nasal neoplasms is beyond the scope of this chapter.

Acute rhinosinusitis

Rhinosinusitis is defined by an inflammation of the mucosa of the nose and paranasal sinusitis. It is classified as acute, subacute and chronic based on the duration of symptoms, *i.e.* >4, 4–12 and >12 weeks, respectively [6]. ARS and sub-ARS share the same infection aetiology and pathophysiology, with obstruction of the dependent sinus outflow (ostiomeatal complex), and are considered together. ARS usually occurs in the setting of recent viral upper respiratory tract infection, but isolated infections of the maxillary sinus are frequently caused by dental caries (figure 7). A radiological study is not usually required. Air-fluid levels, mucosal thickening and soft tissue secretions are findings of ARS, but are not specific. CT findings must be correlated with clinical findings for adequate patient management. Key information provided by imaging are the extent of the disease, presence of anatomical variants altering the drainage of the paranasal sinuses (figure 2) or increasing the risk of intraoperative complications, presence of resorption of the sinusal walls, and assessment of extent and complications. Infection may extend into the orbit through small valveless venous channels that communicate between the orbits and paranasal sinuses. When an orbital complication is suspected, generally secondary to acute ethmoiditis, CT must be

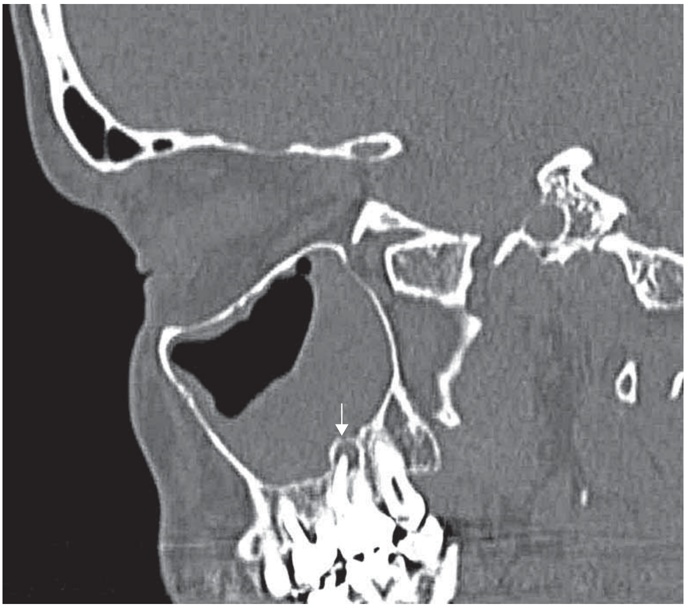

Figure 7. Sagittal high-resolution CT reconstruction of the paranasal sinuses. Note the thickened mucosa almost filling up the sinus. White arrow shows a granuloma developing at the apex of a root of a tooth.

performed with intravenous contrast agent injection, and helps to identify the site of the lesions and to discriminate between pre-septal sinusitis, subperiosteal inflammation and intraorbital (extra- and intraconal) spread. Cellulitis is identified by thickening and increased density of soft tissue, whereas subperiosteal abscesses are identified by a fluid collection with a peripheral enhancing rim and sometimes gas bubbles. Periorbital abscesses are generally observed along the lamina papyracea, displacing the orbit and seen as a rim-enhanced fluid collection. Intraconal extension of the abscess is a key point to identify. Bone changes vary greatly. Intracranial complications, generally secondary to frontal sinusitis, can be observed, even in the absence of any sinus defects, secondary to thrombophlebitis of diploid veins. Vascular complications such as ophthalmic vein or cavernous sinus thrombosis and intracranial complications are better demonstrated by MRI.

Chronic rhinosinusitis

CRS is very commonly encountered in clinical practice. It is defined as the presence of at least two symptoms persisting for a period of >12 weeks, with radiological or endoscopic documentation of inflammation [6]. The symptoms must have persisted for at least 12 weeks. CT is the most frequently used tool in the evaluation of CRS, although the association between imaging findings and symptoms is controversial, with 27–42% of asymptomatic subjects reported with CT findings of chronic paranasal sinus disease [7]. In addition, symptom severity does not correspond with the severity of imaging findings [8]. Paranasal sinus mucosal thickening may not represent inflammatory changes and, in the asymptomatic setting, may be related to submucosal oedema or mucosal secretions. It is therefore essential to consider clinical findings for a proper diagnosis of CRS. CT findings of CRS include mucosal thickening, osseous thickening due to reactive osteitis, sino-nasal polyposis and mucous retention cysts, the latter two being absent in the setting of ARS. Polyps represent benign mucosal hypertrophic protrusions that result from inflammation and infection. They are difficult to differentiate from mucous retention cysts or mucosal thickening on unenhanced CT. They enhance on post-contrast imaging, as opposed to retention cysts and mucoceles that do not. In the setting of polyposis, mucous secretion can collect between and around polyps and, depending on the proteinaceous content of these secretions, can give a mixed attenuation pattern on CT. Chronic remodelling of sinus bony walls manifests as a thickened, partially resorbed osseous structure. Chronic luminal modification of the sinus may also occur, visible as variably attenuated soft tissues. For instance, hyperattenuating material can be due to inspissated mucus, haemorrhage or superimposed fungal infection. Calcifications can be found in the setting of chronic inflammatory changes as well as fungal infection. The latter tends to produce central calcifications, whereas those associated with nonfungal sinusitis are likely to be peripheral with an eggshell configuration. Predisposing anatomical factors that may impair mucociliary drainage are essential features to identify on imaging, in addition to the changes described earlier. Obstruction of the ostiomeatal complex, either by mucosal thickening or isolated polyps, involves the infundibulum and maxillary sinuses, whereas the ethmoid and frontal sinuses are preserved. Anatomical predisposing factors are Haller cells and hypoplasia of the maxillary sinus. Obstruction of the middle meatus is favoured by marked septal deviation and a concha bullosa, and involves the maxillary, frontal and anterior ethmoid sinuses. Sphenoid recess obstruction involving the sphenoid sinus and posterior ethmoid is much less common. Nasal polyposis, involves the middle meati on both sides (figure 5), ethmoid infundibula and paranasal cavities, and appears as solid lobulated lesions filling the nasal and paranasal sinus cavities with bone remodelling and displacement of the lamina papyracea, sometimes associated with widening of the ethmoid infundibulum and truncation of the middle turbinate. The MRI signal pattern does not differ that from mucosal cysts (hyperintense T2 signal and a mixture of hypo- or hyperintense T1 signals). An antro-choanal polyp is a peculiar variant arising from the maxillary sinus and protruding in the middle meatus.

As noted earlier, the association between imaging findings and symptoms is controversial [7], symptom severity does not correspond to the severity of imaging findings [8], and paranasal sinus mucosal thickening may not represent inflammatory changes. Isolated mucosal thickening is unrelated to impairment of the mucociliary pattern, and is extremely frequent and impossible to differentiate from polyps or retained secretions, leading to a partially or complete obliteration of the sinus without bony changes. On MRI, the signal is hyperintense T2 and various T1 depending on protein secretion, with enhancement after gadolinium injection. Retention cysts, mostly observed in the maxillary sinus in the alveolar recess or at the level of the roof and secondary to the obstruction of a mucosal or minor salivary gland, appear as hypodense lesions with a smooth convex border and their signal on MRI is similar to that of retained secretions.

The most widely used imaging scoring system for CT is the Lund–Mackay system [9]. Although reproducible, relationships with clinical findings remain controversial [10].

Fungal sinusitis

Fungi are responsible for simple colonisation or true infection, depending on the immune status of the host, as well as a severity that can be fatal when orbital and cerebral involvement occurs. Based on histology, fungal rhinosinusitis can be divided into invasive and noninvasive groups, with the invasive group being defined by the presence of fungal hyphae within the mucosa, submucosa, bone or blood vessels of the paranasal sinuses [11]. Invasive forms occur in the clinical setting of chemotherapy, human immunodeficiency virus infection and diabetes mellitus, and can be categorised as acute, chronic and granulomatous entities, depending on the course of the disease. Noninvasive fungal rhinosinusitis is defined by mycetoma and allergic fungal rhinosinusitis, and occurs in immunocompetent subjects [12, 13].

A mycetoma is a dense conglomeration of fungal hyphae within a single sinus cavity, usually the maxillary sinus, secondary to a deficient clearance mechanism and is mainly caused by *Aspergillus fumigatus* [14, 15]. A hyperattenuating mass with sometimes metal-dense spots corresponding to fungal waste products is visible on CT. On MRI, the fungus ball is hypointense on both T1- and T2-weighted images, and is surrounded by hyperintense inflamed mucosa on T2-weighted images (figure 6) [14, 16].

Allergic fungal sinusitis is an IgE-mediated hypersensitivity reaction to fungal elements and typically occurs in the clinical setting of allergic rhinosinusitis, known sino-nasal polyposis or asthma. The causative agent is not only *Aspergillus*; other moulds such as *Fusarium* may be involved. On nonenhanced CT, mucin accumulation is responsible for a relatively hyperdense near-complete fill-in of the nose and paranasal cavities. Erosion/remodelling and thinning of bony sinus walls is frequent. On T2-weighted MRI, a low signal intensity mass is attributed to the concentration of metal ions, proteins and low free water content surrounded by hyperintense inflamed mucosa. On T2-weighted MRI, the overlying inflamed mucosa appears relatively hypointense and enhanced upon gadolinium injection. Advanced disease can show infraorbital and cranial extension.

Acute invasive fungal rhinosinusitis has a mortality rate of 50–80% [17], and is caused by *Aspergillus* and fungi in the order *Mucorales*. CT findings are mainly mass effects of the maxillary, ethmoid and sphenoid sinuses, and may extend to facial (figure 8) and orbital soft tissue, and to central nervous system involvement of the cavernous sinus with thrombosis, cerebritis, brain abscess, meningitis, osteomyelitis, mycotic aneurysm and stroke. MRI is helpful to demonstrate extension beyond the paranasal sinuses and other complications [14]. Chronic fungal rhinosinusitis occurs in slightly immunocompromised patients, such as those treated by corticosteroid therapy, or suffering from diabetes mellitus or acquired immunodeficiency syndrome, and shows a prolonged clinical development of >12 weeks. Imaging features are similar to acute invasive fungal rhinosinusitis or to the noninvasive form, or to a combination of both. A hyperattenuating mass with bony wall destruction extending into the adjacent orbit, maxillary floor and hard palate mimicking malignancy is common [14]. Granulomatous invasive fungal rhinosinusitis is a form characterised by the presence of noncaseating granulomas in immunocompetent hosts and a disease course lasting >12 weeks, mostly observed in Sudan, India and Pakistan [17].

Systemic disorders

Granulomatous with polyangiitis affects the respiratory system and the kidneys. A sino-nasal tract localisation is present in up to 91% (figure 9). Imaging shows the presence of mucosal thickening, bony and cartilaginous alteration, resorption or osteogenesis, middle ear or cranial nerve involvement, extension into the deep spaces of the pterygopalatine fossa and masticator space, detection of complicated sinusitis requiring surgical treatment, lacrimal gland involvement, or intraorbital involvement [18]. Sino-nasal involvement is present in <1% of sarcoidosis patients [19], and has also be reported in Sjögren's syndrome and vasculitis

Sino-nasal involvement in airway diseases

Sinus disease has been reported in the context of non-CF bronchiectasis, PCD (Kartagener's syndrome), asthma, allergic bronchopulmonary aspergillosis, COPD, respiratory sleep disorders, *etc.*, and many of these associations are covered in detail in other chapters of this *ERS Monograph* [20]. Sinus disease is ubiquitous in the context of CF and will be specifically addressed in this chapter because of the major benefit of advanced MRI in this patient population, particularly in terms of radiation dose reduction. In the setting of CF, self-assessment *via* clinical scales demonstrates a poor correlation with actual disease burden. On the one hand, the majority of CF subjects do not report symptoms despite active disease [21]; on the other hand, untreated sinus disease may be a source of persistent colonisation by pathogens in direct contact with the tracheo-bronchial tree [22]. The presence of CRS has been correlated with worse respiratory symptoms. However, sinus treatment is likely to be invasive [23], and thus there is currently no consensus on whether nonsymptomatic patients should be treated and how they may be followed up. Multiple imaging scoring systems have been described using CT, with the most widely used being the Lund–Mackay system [9]. Although all scores have been validated as reproducible [10], other studies performed in CF populations demonstrate poor correlation with symptom severity and QoL [21]. Nevertheless, recent advances in CF treatment using ivacaftor

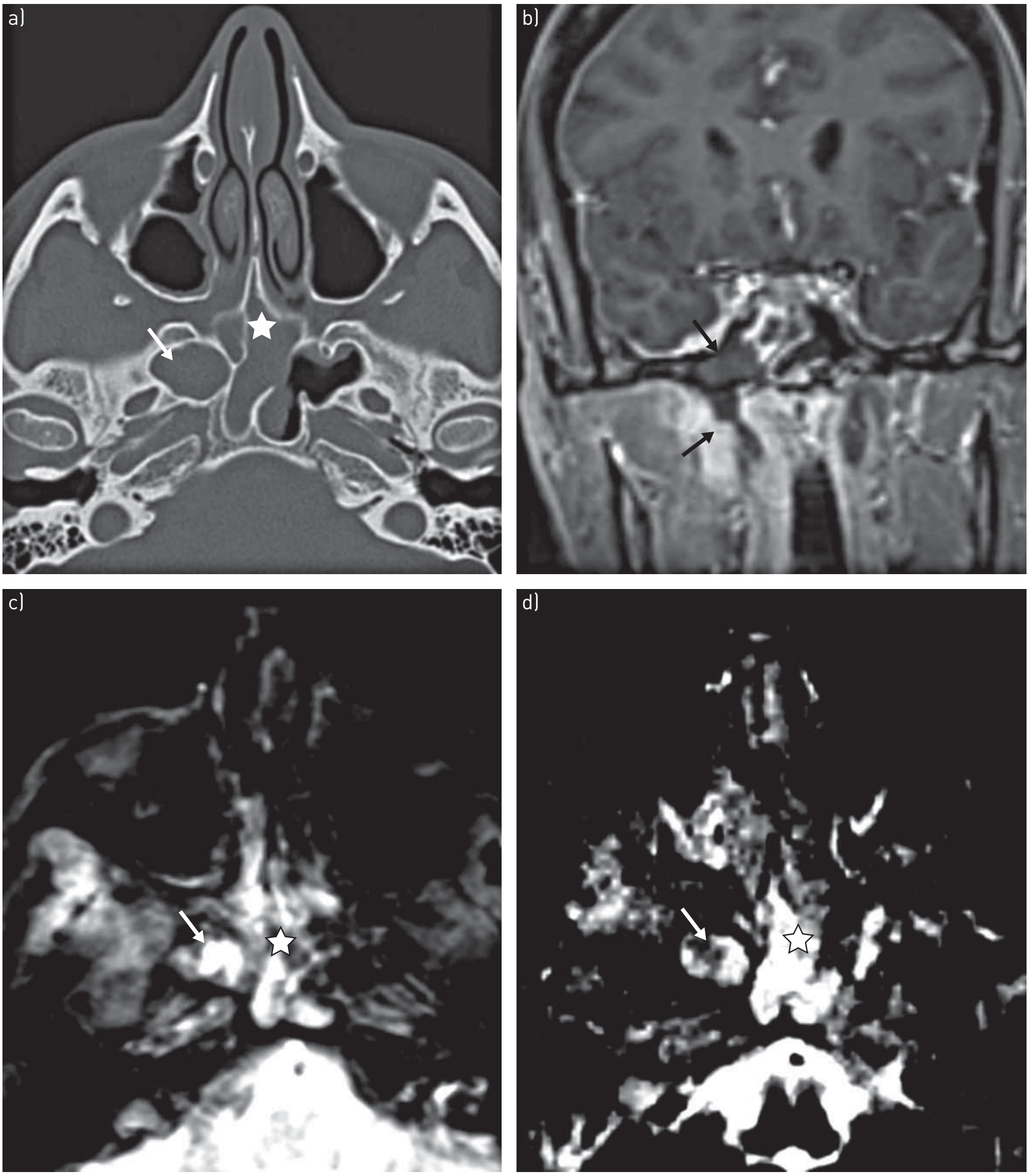

Figure 8. a) Axial high-resolution CT, b) post-contrast T1-weighted MRI with coronal reconstruction, c) axial T2-weighted MRI and d) axial cartography of the apparent coefficient of diffusion using MRI of the sphenoidal sinus in a 20-year-old women. The CT and MRI examinations were performed in the context of leukaemia complicated with headache and fever. White arrows show a complete opacification of both the right and left sphenoidal cells on a) axial CT and c, d) MRI sequences. b) The coronal MRI shows inflammation of both the right sphenoidal sinus and adjacent structures such as the nasopharynx (black arrows). c, d) Characterisation using MRI shows marked restriction of the material within the right sphenoidal cell (white arrows) and is suggestive of an abscess, whereas the left sphenoidal sinus appears with a water-like appearance (white stars). The sole pathogen found in the right sphenoidal cell was *Aspergillus fumigatus*.

therapy have emerged and therefore quantitative scoring of sinus alterations may be useful to assess response to treatment. In this setting, MRI has been shown to be a valuable alternative to CT in sinus imaging. Despite being considered inferior to CT in imaging bone

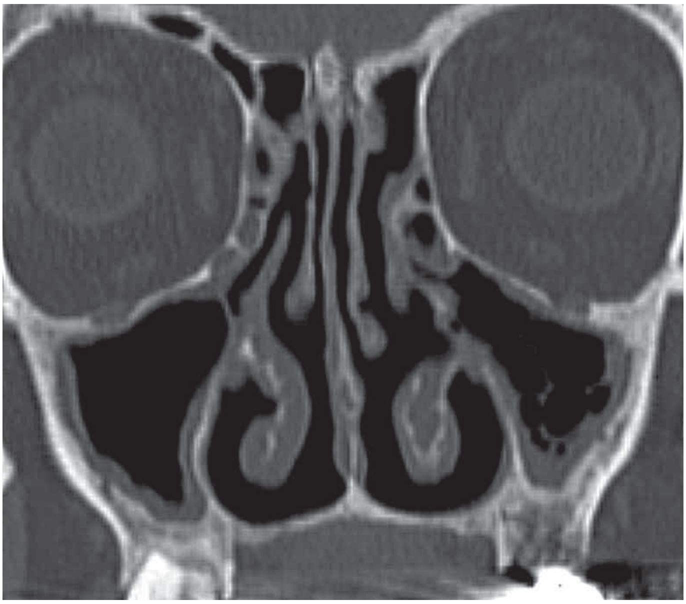

Figure 9. Coronal high-resolution CT reconstruction of the paranasal sinuses in a patient followed up for granulomatosis with polyangitis. Diffuse inflammatory thickening of the mucosa without air-fluid level. The bone layers of the maxillary sinuses are thickened, suggestive of bone remodelling from a chronic inflammatory process.

structures, MRI can show additional contrast information related to mucus and mucosa. For instance, it enables discrimination between mucosal wall thickening and intraluminal mucus, whereas these two features cannot be discriminated using unenhanced CT, especially when the sinus cavity is full [24]. In addition, recent advances in MRI using ultra-short echo time [5] have shown that three-dimensional submillimetre MRI can be performed with a reasonable acquisition time of 2–3 min. Repeated imaging of the sinuses can therefore be performed without radiation exposure for follow-up of novel therapies [25].

Conclusions

In daily practice, CT is currently the best tool for imaging the nose and sinuses in the clinical setting of respiratory diseases. Two rules of thumb should be kept in mind, however: 1) the clinical features should be integrated in CT interpretation, and 2) anatomical variants may have a significant impact on understanding abnormal CT findings and should be described.

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Chapter 4

Nasal and sinus problems in cystic fibrosis patients

Daniel L. Hamilos

CF is an autosomal recessive disorder caused by mutations in the CFTR gene leading to reduced or defective CFTR protein expression and improper salt balance and thick tenacious secretions. There is an increased prevalence of *CFTR* mutations in children and adults with CRS who otherwise do not meet diagnostic criteria for CF and who usually have a normal sweat chloride level. Reduced function of CFTR in CF patients negatively impacts sino-nasal mucociliary clearance due to an increase in the viscosity of sino-nasal epithelial lining fluid, and is associated with reduced airway surface liquid pH, increased baseline nasal potential difference and reduced nasal nitric oxide. Reduced nasal airway surface liquid pH has been causally linked to reduced airway innate immunity by virtue of a detrimental effect on the function of antimicrobial proteins. Newborns with CF already manifest the physiological abnormalities of reduced CFTR function. This chapter provides an overview of sino-nasal involvement in CF patients, in terms of genetics, immunology, pathology and clinical presentation, and discusses management strategies and treatment outcomes.

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CRS is highly prevalent in patients with CF, accounting for significant morbidity and contributing to CF lung disease. Mutations of the CFTR gene are also seen with increased prevalence in non-CF CRS patients, suggesting some contribution to CRS pathophysiology.

Prevalence of CF worldwide

CF is an autosomal recessive disorder affecting roughly 70 000 people worldwide. It is most prevalent in people of Caucasian descent; however, CF can affect nearly every race and ethnicity [1].

The disease is caused by mutations in the CFTR gene leading to reduced or defective CFTR protein expression, improper salt balance and thick tenacious secretions. The CFTR gene is

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located on chromosome 7. The most common mutation, F508del, accounts for ∼70% of CF mutations worldwide, but more than 850 mutant alleles were reported to the CF Genetic Analysis Consortium in 2000 [2]. Even more mutations (approximately 2000) in the CFTR gene have now been identified, although the majority are extremely rare and, to date, only 242 *CFTR* mutations have been confirmed as causing CF [3].

Genetics of CF

Mutations in the CFTR gene are classified into six different classes. Class I mutations result in defective synthesis of the full-length CFTR protein due to premature or nonsense mutations. Class II mutations, including the F508del mutation, result in defective post-translational processing and transport of the CFTR protein to the cell surface. Patients who are homozygous for F508del account for ∼50% of CF patients in the USA [4]. Class III mutations result in disrupted regulation or gating of the chloride channel. Most patients with classic CF have class I, II or III mutations and a severe CF phenotype plus a highly elevated sweat chloride concentration [5]. Class IV mutations result in impaired movement of ions through the chloride channel that may have partial activity *in vivo*. Class V mutations result in a splicing defect that leads to decreased quantities of *CFTR* transcripts, reduced synthesis of CFTR protein and fewer functional CFTR channels at the cell surface. Finally, class VI mutations result in reduced stability and accelerated turnover of CFTR protein and insufficient CFTR at the cell surface [5].

The percentage of normal CFTR activity associated with disease varies by organ system [6]. Pancreatic function is closely related to the specific type of *CFTR* mutation and CFTR channel activity such that mutations with little activity (AF508, G551D) or mutations that result in severe quantitative reduction of CFTR (*e.g.* W1282X) are associated with pancreatic insufficiency. In contrast, in the airways the relationship between genotype and phenotype is less clear, but in general airway physiology is more affected by reduced CFTR function than is the pancreas [6]. An approximation of the percentage of normal CFTR functional activity and CF disease manifestations is shown in table 1.

The terms “variant CF” or “atypical CF” describe patients who have atypical clinical presentations of CF with normal or borderline sweat chloride levels (30–60 mmol·L^{-1}), despite

Table 1. The relationship between the amount of normal CFTR activity and clinical manifestations of reduced CFTR function

Normal CFTR activity %	Clinical manifestations of reduced CFTR function
50–100	Most are asymptomatic (heterozygotes: “carriers”) but an increased prevalence of CRS has been reported in CF carriers
10–49	No known abnormality
<10	Male infertility (congenital bilateral absence of the vas deferens, this is the organ with the greatest requirement for normal CFTR activity)
<5	Clinically demonstrable sweat duct/sweat chloride abnormality
<4.5	Progressive pulmonary disease
<1	Classic CF with pancreatic insufficiency and recurrent respiratory infection

Information from [6–8].

having two CFTR gene mutations [9]. A more comprehensive definition of "atypical CF" was published in the Cystic Fibrosis Foundation consensus report [10], which encompasses those with atypical clinical presentations and either 1) intermediate or abnormal sweat chloride levels, despite lacking two *CFTR* mutations, or 2) normal or intermediate sweat chloride levels and two *CFTR* mutations. As already noted, although around 2000 *CFTR* mutations have been described, only 242 of them are known to cause CF [3]. A typical commercial CF genetic blood test involves testing for 97 mutations (www.genet.sickkids.on.ca).

Genotype–phenotype correlations in CF patients

Berkhout *et al.* [11] found that adult CF patients with class I–III mutations had significantly smaller frontal sinuses and sphenoid sinuses, more opacification in the sino-nasal area, and a higher prevalence of osteitis/neo-osteogenesis of the maxillary sinus wall compared with patients with class IV/V mutations. Ferril *et al.* [12] examined genotype–phenotype correlations in "high-risk" (class I–III) *CFTR* mutations *versus* "low-risk" (class IV/V) *CFTR* mutations. They found that compared with non-CF patients with CRS, the high-risk *versus* low-risk genotype group had a younger age at diagnosis, higher sweat chloride level, higher prevalence of sputum *Pseudomonas aeruginosa* colonisation, higher modified Lund–Mackay score and higher prevalence of aplasia or hypoplasia of one or more sinus cavities. However, the prevalence of aplasia or hypoplasia of one or more sinus was higher in both the low-risk and high-risk CF groups compared with the non-CF CRS control group [12].

Modifier genes of relevance to CF

It has been observed that CF patients manifest a broad range of clinical severity even among patients carrying the same genotype [13]. Several studies have used phenotypic comparisons and/or gene association approaches to examine potential modifier genes in CF (reviewed by Farrell *et al.* [10]). These studies examined a host of candidate genes that might modify CF disease severity by their effects on inflammation, innate immunity or response to infection.

Studies examining the transforming growth factor-β1 gene (*TGFB1*) suggested that it is a modifier of CF lung function, with an association found between the −509C allele and the codon 10T allele with improved lung function [14].

Several studies have implicated variants in mannose-binding lectin (MBL) as an important modifier gene (*MBL2*) in CF; however, not all studies have confirmed this association. In one study, McDougal *et al.* [15] examined 788 patients in the US CF Twin and Sibling Study and found that *MBL2* genotypes corresponding to low levels of MBL were associated with *P. aeruginosa* infection 1.94 years earlier than were *MBL2* genotypes corresponding to high levels of MBL. Furthermore, *P. aeruginosa*-infected patients with *MBL2* genotypes corresponding to low levels of MBL experienced conversion to mucoid *P. aeruginosa* [15]. Gravina *et al.* [16] examined *MBL2* variants in 106 Argentinean paediatric CF patients carrying two severe *CFTR* mutations. MBL insufficiency was associated with a 3.5-fold risk of having a severe phenotype and was associated with an earlier onset of infection with *P. aeruginosa*.

Single nucleotide polymorphisms in the IFN-related developmental regulator 1 gene (*IFRD1*) were examined in CF patients with and without nasal polyps, and the T allele of the common polymorphism rs7817 and the rs7817–rs3807213 haplotype were associated with the presence of nasal polyps [17].

Prevalence of *CFTR* mutations in non-CF adults and children with CRS

Wang *et al.* [7] performed a case–control study of 147 unselected CRS adult patients and 123 CRS-free adult Caucasian control subjects examining each subject for the presence of 16 mutations known to account for 85% of CF alleles in the general population. The prevalence of a single CF mutation in CRS patients was 7%, whereas that in the control population was 2%. Nine of the 10 CF carriers had the M470V polymorphism [7]. This study suggested that mutations in the CFTR gene may be associated with the development of CRS in the general population. Investigators from this group also examined a cohort of 147 obligate CF carriers (parents of patients with CF) and found that 36% of them had self-reported CRS. In ~50% of those self-reporting CRS, the diagnosis of CRS was confirmed and thus it was concluded that carriers of a single CF mutation have a higher prevalence of CRS than the general population [8].

Similarly, Raman *et al.* [18] examined the prevalence of *CFTR* mutations in a cohort of 58 Caucasian children with CRS. Children were tested for 87 mutations that account for 90% of CF mutations seen in individuals of northern European ancestry. They found that 12.1% of the patients had *CFTR* mutations compared with the expected rate of 3–4% in this ethnic group. Only one of these had a borderline abnormal sweat test. Their results confirmed the findings of Wang *et al.* [7] in an adult population, *i.e.* that there is an increased prevalence of *CFTR* mutations in children with CRS who otherwise do not meet diagnostic criteria for CF and who usually have a normal sweat chloride level.

CFTR defects impact on mucociliary clearance

The physiological effect of alterations in the transepithelial passage of anions (chloride and bicarbonate) through the sino-nasal epithelium due to dysfunctional chloride channels in CF is to increase the viscosity of the sol phase of the sino-nasal epithelial lining fluid. As a result, the normally low-viscosity periciliary fluid layer (sol) beneath the superficial mucus (gel) layer is 30–60 times more viscous than normal, resulting in a marked disruption of normal mucociliary clearance [4]. The tenacious secretions lead to sinus ostial obstruction, hypoxia and oedema with resultant bacterial infection. Chronic bacterial infection and a vigorous host inflammatory response damage the lungs and cause loss of pulmonary function. Large amounts of DNA released from the degeneration of neutrophils contribute to the high viscosity of airway secretions in patients with CF [19].

CFTR mRNA expression occurs pre-natally, and progression of disease in the respiratory and digestive tracts in infants as young as 6 months of age, and progressive functional declines occurring yearly in the first 6 years of life have been observed [20]. There are several studies demonstrating that CF children with access to earlier routine CF care have better outcomes compared with children without such access, including reduced airway inflammation, lower incidence of mucoid *P. aeruginosa* colonisation, improved growth, reduced hospitalisations and improved survival (reviewed by VanDevanter *et al.* [20]).

Reduced airway surface liquid pH, nasal potential difference and nasal nitric oxide in CF patients

Reduced nasal pH

The CFTR channel conducts chloride and bicarbonate anions. Abou Alaiwi *et al.* [21] found that neonates with a positive immunoreactive trypsinogen (IRT) (⩾65 ng·mL^{-1}) screening test for CF had a reduced nasal airway surface liquid (ASL) pH (pH 5.2±0.3) *versus* non-CF neonates (pH 6.4±0.2). In contrast, the nasal pH values of CF children and adults were similar to those measured in subjects without CF, possibly due to alterations in nasal ASL caused by secondary effects of CF nasal and sinus disease. The reduced nasal pH has important relevance to sino-nasal innate immunity (as discussed later in this chapter).

Nasal potential difference

Nasal potential difference (NPD) is frequently used as a diagnostic and research tool for CF in CF centres by the European Cystic Fibrosis Society [22]. It is a measurement of nasal transepithelial potential difference. Ion transport defects caused by *CFTR* mutations lead to an abnormal transepithelial potential difference.

Patients with CF have increased sodium ion absorption, reflected by the increased negative basal potential difference, and absent or reduced CFTR-mediated chloride secretion, reflected as absent/decreased response to chloride-free and isoproterenol solutions. Following perfusion with amiloride, an epithelial sodium channel (ENaC) blocker, the nasal lumen becomes less negative in CF as sodium ion absorption by the cells is blocked, but more negative in healthy, non-CF patients. When a chloride-free solution is perfused, causing chloride anion secretion out of the cells, a rapid and often large increase in negative potential difference follows in non-CF patients (a result of intact CFTR-mediated chloride secretion) but not in CF patients. Significant differences in NPD can therefore be seen in CF patients *versus* healthy, non-CF patients at baseline and following perfusion with amiloride, chloride-free solution and isoproterenol (reviewed by Ooi *et al.* [23]).

Patients with CF typically have a basal NPD of −30 mV or higher and a chloride-free/isoprenaline response of −5 to −10 mV or less. Patients with mild or atypical forms of CF have intermediate values which may or may not correlate with the results of their sweat chloride measurement [24]. A study by Valiulis *et al.* [25] in children found similar results, with children with a clinical diagnosis of CF having an NPD of −28.0±10.2 *versus* −15.5 ±4.3 mV in healthy children and −18.1±3.6 mV in children with non-CF obstructive lung disease.

NPD has been studied as a diagnostic modality potentially useful in cases of CF that are not clear-cut, such as in patients presenting at an older age with single-organ manifestations of CF. Ooi *et al.* [26] found that in such cases, extensive genotyping may fail to confirm the diagnosis of CF and there can be discordance between sweat testing and NPD. In their study, discordance between sweat chloride and NPD was found in 14%, 33% and 28% of patients with sino-pulmonary diseases, pancreatitis and obstructive azoospermia, respectively [26]. In a follow-up study, the same group studied the use of a combined ion channel measurement (C-ICM) technique which combined sweat chloride measurement with two NPD parameters [23]. In borderline sweat test cases, the investigators found that

23.5%, 90% and 100% of subjects had abnormal C-ICM values with normal, borderline and abnormal NPD, respectively. This suggests that utilisation of C-ICMs can be useful in the diagnostic determination of patients with questionable CF.

NPD has also been used as an end-point in clinical trials to measure the restoration of CFTR function [27]. Figure 1 summarises derangements in the nasal epithelium and nasal ASL resulting from loss of function of CFTR in CF patients.

Nasal nitric oxide

Nasal nitric oxide (nNO) levels have been found to be low in several studies in children and adults with CF, although the mechanism for reduced nNO levels is unclear [28–32]. In children with CF, the presence of nasal polyps was found to be associated with significantly lower nNO levels than in CF children without nasal polyps [33]. Following functional endoscopic sinus surgery (ESS) with removal of nasal polyps, nNO levels were found to increase significantly, but not to normal levels. Low nNO levels were also associated with *Staphylococcus aureus* colonisation in the oropharynx and lower airways [33]. Considering the importance of nNO in normal host defence against bacterial infection, it would be interesting to understand the mechanism for reduced nNO in CF and whether nNO levels can be modulated by CF-targeted therapies or other novel strategies.

CFTR defects impact on sino-nasal innate immunity

Insights into the impact of CFTR defects on innate immunity have been hampered by the lack of a suitable mouse model that replicates human CF [34]. To overcome this obstacle,

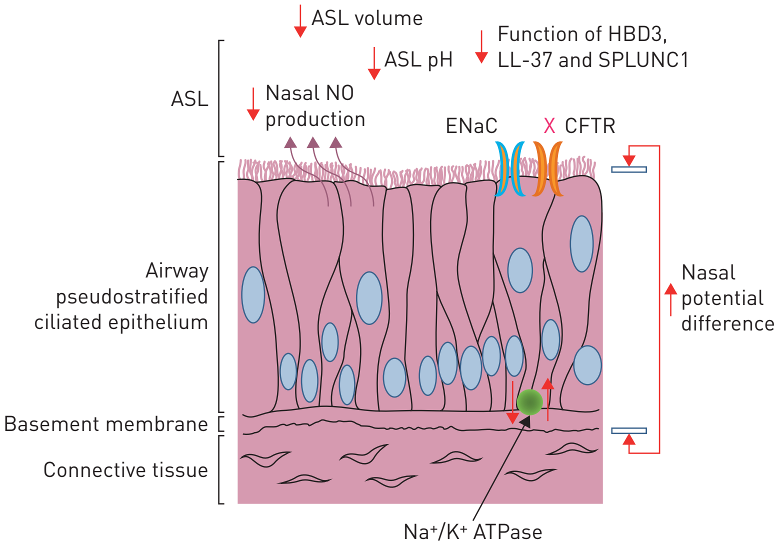
↓ ASL volume
↓ ASL pH
↓ Function of HBD3, LL-37 and SPLUNC1
ASL
↓ Nasal NO production
ENaC
X CFTR
Airway pseudostratified ciliated epithelium
↑ Nasal potential difference
Basement membrane
Connective tissue
Na+/K+ ATPase

Figure 1. Summary of derangements in the nasal epithelium and nasal airway surface liquid (ASL) resulting from loss of function of CFTR in CF patients. Although the epithelial sodium channel (ENaC) receptor protein is normal in CF, the decrease in ASL pH relative to healthy ASL is sufficient to disrupt SPLUNC1's contact with ENaC, thereby allowing ENaC to hyperabsorb sodium ions and water, causing ASL dehydration and mucostasis (see main text for details). NO: nitric oxide; HBD3: human β-defensin-3.

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a pig *CFTR*$^{-/-}$ knockout model was developed [35]. In this model, it was found that CF pigs spontaneously develop hallmark features of CF lung disease, including airway inflammation, remodelling, mucus accumulation and infection. Furthermore, newborn CF pigs fail to eradicate bacteria as effectively as wild-type pigs after intrapulmonary bacterial challenge, suggesting that this failure could initiate a cascade of inflammation and pathology in CF lungs [34]. Using this model, PEZZULO *et al.* [36] immobilised bacteria on grids applied to the airway surface *in vivo* and quantified bacterial killing. They found that CF airway epithelia exhibited a bacteria killing defect independent of mucociliary clearance, phagocyte killing or inflammation. The killing defect was found to be due to impaired bicarbonate anion transport that produced decreased ASL pH in CF airway epithelia, resulting in impairment in the function of antimicrobial proteins in the ASL [36].

The CF pig model has also proven useful for the study of sinus development and sinus physiology. Newborn CF pigs have sinus hypoplasia and spontaneously develop CF sinus disease similar to that of humans with CF [37]. The CF pig model can also be used for performing longitudinal studies of endoscopy, bronchoscopy, microbiological cultures and radiological imaging from birth and throughout the disease. In contrast, studies in humans with CF are often confounded by the advanced stage of sinus disease with associated inflammation and infection.

In vitro studies mixing *CFTR*$^{-/-}$ and *CFTR*$^{+/+}$ epithelial cells in various proportions confirmed that increasing CFTR expression results in progressively enhanced (normalised) ASL pH and correction of epithelial innate defence properties [38, 39]. To assay ASL antimicrobial activity, a small gold grid with attached bacteria was used *in vivo* or *in vitro* with subsequent quantification of the percentage of nonviable bacteria on the grid. Using this technique, the investigators observed pH-dependent killing of *S. aureus* as well as *P. aeruginosa*.

The study by ABOU ALAIWA *et al.* [38] found that the activities of ASL human β-defensin-3 and the cathelicidin-related peptide LL-37 in killing *S. aureus* were both affected by reducing the ASL pH from 8.0 to 6.8. An acidic pH also attenuated the ability of LL-37 to kill *P. aeruginosa*. In addition, this study identified synergism between the bacterial killing capacity of human β-defensin-3 and LL-37 for killing *S. aureus*, synergism between LL-37 and lysozyme bacterial killing, and reduced synergism in an acidic pH [38].

Another key antimicrobial factor in ASL, SPLUNC1 (now identified as human BPI fold containing family A member 1 (*BPIFA1*)) is a member of the family of PLUNC (palate, lung and nasal epithelium clone) proteins expressed in the upper respiratory tract and oral cavity that has antimicrobial properties. SPLUNC1 has been shown in pulmonary infection models to have antimicrobial properties against *Mycoplasma pneumoniae*, *P. aeruginosa* and *Klebsiella pneumoniae*, and nontypeable *Haemophilus influenzae* and *Burkholderia cepacia* [40, 41].

Levels of SPLUNC1 were found to be significantly increased by immunostaining in CF in diseased small airways compared with similar sized airways in non-CF lungs where staining was absent [42]. No alveolar epithelial staining was noted in CF tissue.

SPLUNC1 protein, however, appears to be multifunctional. In addition to its antimicrobial properties, it has also been shown to modulate ASL homeostasis by acting as an endogenous inhibitor of ENaC. TARRAN and REDINBO [43] proposed that SPLUNC1 serves to plug the operational ENaC "drain" that removes sodium ions and water from the ASL overlying airway epithelia. At normal pH in healthy lungs, SPLUNC1 can effectively contact ENaC and prevent the proteolytic activation of this channel. However, in CF the decrease in ASL pH relative to healthy ASL is sufficient to disrupt SPLUNC1's contact with ENaC, thereby allowing ENaC to remove sodium ions and water, and causing ASL dehydration and mucostasis [44]. In support of this, it was shown that elevation of CF ASL pH prevents cleavage of ENaC and restores ASL volume homeostasis [44]. The complete SPLUNC1 molecule appears essential in pH-dependent ENaC control [43].

One of the most exciting potential uses of the CF pig model is in testing the effects of systemic or topical therapy on sinus function, including effects on sinus innate immune function and control of sinus infection (reviewed by Chang [45]). The CF pig can also be used to test therapies before the onset of disease when treatment may be more effective, and to ask questions such as whether bicarbonate anion delivery to the airway that corrects the abnormally low ASL pH restores antimicrobial activity and helps prevent or eradicate airway infection in CF.

Role of defective autophagy in CF

Autophagy has emerged as a key intracellular process for maintaining cellular homeostasis and energy balance [46]. Airway epithelial cells in CF patients and a mouse model of CF were discovered to be autophagy deficient with highly reduced autophagosome formation, a defect in mitochondrial membrane depolarisation and accumulation of the ubiquitin-binding adaptor molecule SQSTM1/p62 (sequestosome 1 (*SQSTM1*)) [47–49]. The defective autophagy was also confirmed to be present in CF macrophages [47]. In newborn mice bearing the F508del *CFTR* mutation, orally administered cysteamine (the reduced form of cystamine) was shown to restore autophagy function and rescue the functional expression of CFTR at the respiratory epithelial surface, reduce lung inflammation and reduce mortality in F508del homozygous mice [50]. In parallel experiments using nasal epithelial cells from F508del homozygous CF patients, cysteamine was also able to increase the plasma membrane expression of the F508del CFTR protein *ex vivo* [50]. These studies offer promise for novel drug treatment strategies to restore CFTR function in F508del homozygous CF patients.

Pathological basis and distinct pathological features of CRS in CF patients

In 1979, Oppenheimer and Rosenstein [51] described the features of nasal polyps from CF patients as a "triad" of delicate, barely visible basement membrane of surface epithelium without submucosal hyalinisation, lack of extensive infiltration of eosinophils (Giemsa stains), and a preponderance of acid mucin in glands and cysts of the polyp and in its surface mucous blanket based on Alcian Blue–periodic acid–Schiff staining. By comparison, nasal polyps in adult non-CF patients were described as having the reverse triad of extensive thickening of the epithelial basement membrane and its extension into the submucosa as an irregular hyaline membrane, high stromal eosinophil counts, and mainly neutral mucin in mucous glands, cysts and mucous blanket [51]. These characteristic features of non-CF nasal polyps have withstood the test of time [5].

Schraven *et al.* [52], in a single-centre prospective observational study of 81 paediatric CF patients aged $\leqslant$18 years, found that 19.8% of their CF patients underwent functional ESS because of CRS. The prevalence of polypoid CRS was 18% in infants aged <6 years and increased to 45% in adolescents aged 13–18 years. The histology of polypoid lesions in this population typically showed dilated glandular ducts and a predominance of mucous glands with an increased number of plasma cells and mast cells. The number of eosinophils was in the range of 1–50 per field, which was lower compared with a group of non-CF patients of comparable age with "idiopathic" polypoid CRS [52]. A study by Steinke *et al.* [53] of nasal polyps from 12 CF patients found that 42% of the nasal polyps had an eosinophilic infiltrate, of which 80% had an additional mixed neutrophilic infiltrate. Of the remaining polyp samples, 16% were neutrophilic, but not eosinophilic, and 42% did not have a neutrophil or eosinophilic infiltrate, consistent with noneosinophilic polyps. All samples had CD138$^+$ plasma cells [53].

Sinus mucosal specimens from functional ESS were examined for the presence of T-lymphocytes, eosinophils, macrophages, neutrophils and inflammatory cytokines using *in situ* hybridisation. Compared with non-CF adult patients, the CF patient mucosal specimens had higher numbers of neutrophils, macrophages, and cells expressing mRNA for IFN-γ and IL-8, whereas the number of eosinophils and cells expressing mRNA for IL-4, IL-5 and IL-10 was higher in non-CF CRS patients. It was not stated whether any of the subjects in this study had nasal polyps [54].

Newborn CF screening and impact of CF on nasal and sinus disease in newborns and infants

In the USA, CF occurs in 1:2500–3500 Caucasian newborns and is less common in other ethnic groups, affecting about 1:17 000 African-Americans and 1:31 000 Asian-Americans [55]. The allele frequency of the mutant CFTR gene among Caucasians is 0.025 [56]. Newborn screening for CF is now performed in all 50 states in the USA, although the testing methodology varies by state [57]. Screening starts with a blood test from the newborn to measure pancreatic IRT. IRT levels tend to be high in CF, but elevated IRT levels can also occur as a result of prematurity or a stressful delivery. A high IRT level sometimes occurs when a newborn is a carrier of CF. Some states also perform genetic newborn screening for CF. Babies with no CFTR gene mutations but a high IRT level are unlikely to have CF. Based on the results of screening tests, the parents may be advised to have their infant undergo a sweat test to confirm the diagnosis of CF. In 2013, 60% of new diagnoses of CF in the USA were detected by newborn screening [57].

Clinical presentation of CRS in CF patients

The prevalence of CRS in patients with classic CF approaches 100% [58]. Despite the high prevalence of CRS by radiographic criteria in CF patients, both children and adults, it has been observed that CF patients with extensive sino-nasal disease, including widespread sino-nasal polyposis, sinus opacification, nasal opacification and sinus hypoplasia, can be either minimally symptomatic or even asymptomatic [59, 60].

CF patients underreport CRS symptoms, since only 10–15% of CF patients complain of CRS symptoms even though the majority of CF patients fulfil criteria for CRS [61, 62]. The reason is unclear. Nasal polyps are rare in children <6 years old, but can occur in CF children at any age, with the youngest being 2.5 years old [63]. Those without polyposis have headache as a major complaint, whereas those with polyposis complain more of nasal obstruction unless a mucocele is present [58].

In a study of 63 Irish adults with CF attending a specialist clinic, Casserly *et al.* [64] found that 52% of patients had no symptoms of CRS, whereas 80% of patients had evidence of CRS on nasal endoscopy and 98% of patients had abnormalities on sinus CT scan. Furthermore, there was no significant difference between symptomatic and asymptomatic CF groups with respect to their Lund–Kennedy endoscopic score or their Lund–Mackay CT score [64]. It is somewhat reassuring that Bock *et al.* [65] found that the primary nasal symptoms of "nasal obstruction", "sneezing", "runny nose", "thick nasal discharge" and "reduced sense of smell" from the Sino-Nasal Outcome Test (SNOT)-20 instrument were the SNOT-20 symptoms most highly correlated with rhinoscopically detected polyposis and sino-nasal secretion.

When to suspect CF in children or adults with CRS

Clues to the presence of underlying CF in children or adults with CRS include onset of nasal polyps in a child <6 years of age, the presence of *P. aeruginosa*, *B. cepacia* or *Achromobacter (Alcaligenes) xylosoxidans* sinus or lung infection and the presence of chronic lung infection or bronchiectasis, especially in combination with pancreatic insufficiency, poor nutrition and/or chronic diarrhoea [10]. In addition, an atypical nasal polyp pathology with a paucity of eosinophils and increased neutrophils is also suggestive of underlying CF [52].

Distinct imaging features of CRS in CF *versus* non-CF patients (including unusual manifestations)

A higher incidence of underdeveloped sinuses in adult CF patients has been reported. Woodworth *et al.* [66] found that F508del homozygotes had a significantly higher prevalence of underdeveloped sinuses compared with a "CF control group" with other mutations, including an increased frequency of underdeveloped frontal (98%), maxillary (70%) and sphenoid (100%) sinuses compared with CF patients with other mutations (69%, 8% and 50%, respectively) [66]. Whether these increases reflect an increased frequency of sinus infections or an independent phenotypic expression of F508del homozygosity itself remains unknown. Similarly, Seifert *et al.* [67] found that the F508del mutation was correlated with poorer sinus pneumatisation. In adult CF patients, Orlandi and Wiggins [68] found that 65.9% of the frontal sinuses were either aplastic or hypoplastic, 74.2% of sphenoid sinuses were poorly developed and 84.4% of patients had evidence of bone sclerosis in their sinus walls. In a systematic review of 18 published studies, Kang *et al.* [69] found that the most commonly reported abnormalities were opacification of the sinuses, presence of frontal and sphenoidal aplasia or hypoplasia, underdevelopment of the paranasal sinuses, and medial bulging of the lateral nasal wall on CT scans. Furthermore, bone sclerosis of the maxillary sinus was found in 81.1% of CF patients [68]. Curiously, sinus pneumatisation variants that are commonly observed in non-CF patients are not commonly observed in CF patients with two identified mutations. For example, infraorbital Haller cells and concha bullosa deformities were not observed in homozygote CF patients [70].

Likewise, Berkhout *et al.* [11] found that adult patients with class I–III mutations (usually associated with absence or minimal chloride channel function and a severe phenotype of

CF) had a prevalence of rhinosinusitis of 63% and prevalence of nasal polyps of 25%. Also, in comparison with CF patients with class IV/V mutations, patients with class I–III mutations had significantly smaller frontal and sphenoid sinuses, more opacification in the sino-nasal area, and more osteitis/neo-osteogenesis of the maxillary sinus wall.

Figure 2 summarises the distinctive clinical, radiographic, microbiological and histological features of CRS in patients with CF. A summary of distinguishing features of CRS in CF patients *versus* non-CF patients is presented in table 2 [71].

Management strategies and treatment outcomes

Medical management strategy and treatment outcomes

The key components of medical management were recently reviewed [71]. Mainstays of medical treatment include isotonic saline irrigations and topical intranasal glucocorticoids with some evidence that topical intranasal glucocorticoids reduce nasal polyp size. Although inhaled hypertonic saline (7%) has been widely studied as a mucolytic agent for CF lung disease, there are no reports of its use in CF CRS. Mucolytics have also not been studied as a treatment for CRS in CF and most evidence does not support their use for CF lung disease.

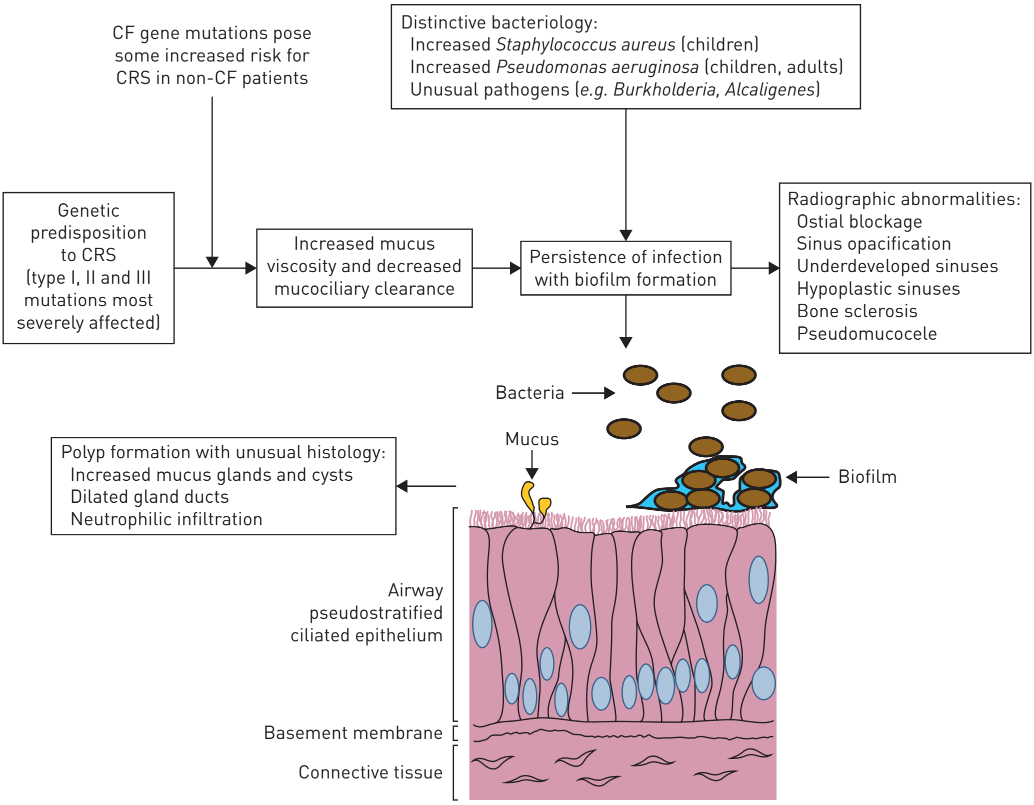
CF gene mutations pose some increased risk for CRS in non-CF patients
Distinctive bacteriology:
Increased *Staphylococcus aureus* (children)
Increased *Pseudomonas aeruginosa* (children, adults)
Unusual pathogens (*e.g. Burkholderia, Alcaligenes*)
Genetic predisposition to CRS (type I, II and III mutations most severely affected)
Increased mucus viscosity and decreased mucociliary clearance
Persistence of infection with biofilm formation
Radiographic abnormalities:
Ostial blockage
Sinus opacification
Underdeveloped sinuses
Hypoplastic sinuses
Bone sclerosis
Pseudomucocele
Bacteria
Mucus
Biofilm
Polyp formation with unusual histology:
Increased mucus glands and cysts
Dilated gland ducts
Neutrophilic infiltration
Airway pseudostratified ciliated epithelium
Basement membrane
Connective tissue

Figure 2. Summary of the distinctive clinical, radiographic, microbiological and histological features of CRS in patients with CF. Reproduced and modified from [71] with permission from the publisher.

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Table 2. Distinguishing features of CRS in CF patients *versus* non-CF patients

Feature	CF patients	Non-CF patients
Prevalence	Adults 65% [11]; approaching 100% in children [59]	12.5% [72]
Prevalence of polypoid CRS		
Infants <6 years	18% [52]	Approaching 0%
Adolescents 13–18 years	45% [52]	7–18.8% [73–75]
Histology of polypoid lesions	Typically show dilated glandular ducts and a predominance of mucous glands with an increased number of plasma cells and mast cells; increased neutrophils and macrophages and cells expressing mRNA for IFN-γ and IL-8 [52, 54]	Typically oedematous with a paucity of glands and a predominance of eosinophils and cells expressing message for IL-5 and IL-13 [72]
Radiographic features	Underdeveloped frontal, maxillary and sphenoid sinuses [66, 67]; frontal sinuses either aplastic or hypoplastic (65.9%) [68]; bone sclerosis in their sinus walls (84.4%) [68]; sinus pneumatisation variants are rarely seen [70]; mucocele formation [68, 76]	Normal sinus development; bone sclerosis in minority of cases; sinus pneumatisation variants are commonly seen (such as Haller cells or concha bullosa); mucocele formation is rare

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Nasally nebulised dornase alfa (recombinant human DNase) following sinus surgery shows promise for treatment. Dornase alfa, which cleaves DNA released in high concentrations by degraded neutrophils in CF mucus contributing to increased mucus viscosity, reduces sputum viscosity, slows the decline in lung function and reduces pulmonary exacerbations in CF patients [77]. Cimmino *et al.* [19] performed a double-blind placebo-controlled trial of 24 patients with CF and CRS in which each patient first underwent sinus surgery and then, starting 1 month after surgery, began treatment with once-daily doses of nasally nebulised dornase alfa or isotonic saline (5 mL) for 12 months. The patients underwent four consecutive treatment cycles, each cycle consisting of 8 weeks of once-daily dornase alfa (2.5 mg in 2.5 mL of vehicle) (Pulmozyme; Genentech, San Francisco, CA, USA) separated by 4-week washout periods. Both therapies were iso-osmolar and administered intranasally *via* a nebuliser. The primary outcome measures were nasal-related symptoms and nasal endoscopic appearance. Both primary outcomes were improved at 24 and 48 weeks in the group receiving dornase alfa, and only at 12 weeks in the group receiving placebo. The secondary outcome measure of FEV_1 was also significantly improved in the patients receiving dornase alfa relative to patients receiving placebo [19].

Mainz *et al.* [78] examined dornase alfa *versus* isotonic saline alone delivered to the sinuses with a Pari-Sinus device (PARI Respiratory Equipment, Midlothian, VA, USA) that delivers vibrating aerosol in 23 CF patients in a crossover treatment study. Only 43.5% of the patients in this study had undergone previous sinus surgery. Each subject received active drug or placebo for 28 days, then underwent a 28-day washout and then were crossed-over to the alternative treatment for 28 days. The primary outcome parameter was primary nasal symptom score derived from the SNOT-20. Sino-nasal dornase alfa treatment was associated with significant improvement in the primary nasal symptoms compared with isotonic saline alone. Additionally, this treatment, but not isotonic saline, was associated with a significant improvement in pulmonary function (forced expiratory flow at 25–75% of forced vital capacity). This treatment has also been studied in one US study that reported improvement in chronic sinusitis symptom scores without improvement in sinus CT scores, endoscopic scores, QoL or lung function [79]. It is not approved by the US Food and Drug Administration (FDA) for use in CRS.

There are no data to support the use of low-dose oral macrolide antibiotics or the use of prophylactic oral antibiotics for CRS in CF patients. However, there are studies supporting the use of topical antibiotics, including colistimethate sodium or tobramycin, administered as a saline irrigation or antral lavage in patients following sinus surgery when susceptible bacteria are cultured [80–82].

A summary of key aspects of medical treatment for CRS in CF patients is presented in table 3 [71].

Surgical management strategy and treatment outcomes

Surgical management strategies and treatment outcomes were also recently reviewed, including the timing of sinus surgery following lung transplantation [71]. Most publications on ESS represented case series, but some of these derived from CF centres with extensive surgical experience and represented "best practice" recommendations intended to limit the need for repeated surgical procedures and improve outcomes in these patients. Several studies reported the benefits of more extensive sinus surgery in CF patients compared with the usual functional ESS performed in non-CF patients to ensure that the maxillary, frontal, sphenoid and ethmoid sinuses are all widely opened with smoothing of bony overhangs to prevent mucus retention and bacterial recolonisation, post-operative

Table 3. Key aspects of medical treatment for CRS in CF patients

Useful therapies include:
- Isotonic saline irrigations (large volume)
- Topical intranasal glucocorticoids are beneficial and may help reduce nasal polyp size
- Nasally nebulised dornase alfa (although not approved by the US Food and Drug Administration for treatment of CRS)
- Culture-directed systemic or oral antibiotics to treat sinus pathogens isolated at the time of endoscopic sinus surgery
- Topical antibiotic irrigation with mupirocin, colistimethate sodium or tobramycin following sinus surgery when susceptible bacteria are cultured

Unproven (or unstudied) therapies include:
- Hypertonic saline irrigations
- Addition of baby shampoo to isotonic saline
- Long-term low-dose oral macrolide antibiotics
- Long-term prophylactic oral antibiotics

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meticulous daily nasal irrigations, and appropriate use of culture-directed topical antibiotics.

A summary of key aspects of surgical treatment for CRS in CF patients is presented in table 4 [71].

Combined medical and surgical management and treatment outcomes

Moss and King [82] performed an open-label trial of a long-term management approach by combining endoscopic surgery with serial antimicrobial lavage (ESSAL) in a group of 32 adult CF patients comparing the results with those in a group of 19 CF patients who underwent conventional sinus surgery without serial antimicrobial lavage. The ESSAL approach incorporated pre-operative nasal endoscopy and CT, endoscopic surgery, a post-operative course of antral antimicrobial lavage (typically consisting of tobramycin in patients infected with an aminoglycoside-sensitive *P. aeruginosa*), and monthly maintenance antimicrobial lavage *via* brief antral catheterisation. The two groups were similar at baseline, with nasal polyposis present in 34% and 42%, respectively. The ESSAL group had fewer operations per patient, fewer Caldwell–Luc procedures, and a decrease in repeated surgery at 1-year (10% *versus* 47%) and 2-year (22% *versus* 72%) follow-up.

Aaenes *et al.* [80] routinely place their CF patients following surgery on 2 weeks of broad-spectrum intravenous antibiotics against the expected bacteria; a minimum 6 months of topical nasal glucocorticoids (mometasone furoate); a minimum of 6 months of daily nasal irrigations with saline and antibiotics (colistimethate sodium when susceptible bacteria are cultured); and conduct post-operative follow-up visits at 1 week and 1, 3 and 12 months when crusts and secretions are endoscopically removed. Virgin *et al.* [81] routinely place post-surgical patients who culture *S. aureus* on mupirocin (3–4 mg, compounded or ointment form) and use topical tobramycin or equivalent for patients who culture *Pseudomonas* species. Once healed from surgery, patients are kept on medicinal/mechanical irrigations and have follow-up debridements to reduce the severity of exacerbations, help keep mucus cleared and decrease the bacterial burden.

Table 4. Key aspects of surgical treatment for CRS in CF patients

Most data regarding ESS in CF patients come from retrospective studies and case series
CF patients have a greater burden of pre-operative sinus disease on sinus CT compared with non-CF patients [83]
The rate of revision ESS is higher in CF patients than in non-CF patients
The rate of revision ESS is higher in CF patients with *versus* those without extensive polyposis
A study comparing ESS *versus* ESSAL reported improved outcomes and a decrease in repeat surgery in the ESSAL treated patients [82]
Most studies of ESS in CF patients do not show a sustained benefit on the level of pulmonary function or pulmonary morbidity
Most experts recommend extensive surgery to ensure that the maxillary, frontal, sphenoid and ethmoid sinuses are all widely opened with smoothing of bony overhangs to prevent mucus retention and bacterial recolonisation coupled with post-operative meticulous daily nasal irrigations

ESS: endoscopic sinus surgery; ESSAL: endoscopic surgery with serial antimicrobial lavage. Reproduced and modified from [71] with permission from the publisher.

Effects of CF-targeted therapies on CRS outcomes

Ivacaftor (Kalydeco; Vertex Pharmaceuticals, Cambridge, MA, USA), which potentiates mutant CFTR already present on the cell surface, was found to cause a significant improvement in lung function and other outcomes in clinical trials in CF patients with the G551D *CFTR* mutation [84, 85]. It is approved by the US FDA for CF patients aged ⩾6 years with at least one copy of this mutation [84]. In a phase II study in CF patients, patients treated with ivacaftor achieved CFTR activity equivalent to ∼35–40% of normal activity [86]. To date, there have been no studies evaluating the effects of ivacaftor on symptoms or objective measures of CRS. Curiously, a single case report of ivacaftor use in a CF patient with a heterozygous F508del/S1251N mutation reported a marked stabilisation of the patient's declining lung function and complete resolution of sinus opacification on the patient's sinus CT scan, and improvement in symptoms of sino-nasal disease [87]. The S1251N mutation is a class III mutation resulting in a defective CFTR protein on the apical membrane. This is interesting, because a study of CFTR channel activity using a Fischer rat thyroid cell model reported that ivacaftor not only potentiated the mutant G551D CFTR channel, but also several other type III "CFTR gating" mutations, including the S1251N mutation.

A second CFTR modulator, which is a combination of ivacaftor and lumacaftor (Orkambi; Vertex Pharmaceuticals), was approved by the US FDA on July 2, 2015 for CF patients ⩾12 years old who have two copies of the F508del mutation, which accounts for ∼50% of CF patients [4]. The F508del mutation prevents the CFTR from achieving the correct shape and reaching the cell surface. Lumacaftor facilitates the movement of defective CFTR protein to its proper place on the cell surface, whereas ivacaftor increases the activity of the defective protein on the cell surface, thereby helping to support the function of the chloride channel.

To date, there are no data on whether the CF-targeted therapies, including ivacaftor or ivacaftor combined with lumacaftor, have an impact on CF CRS.

Conclusions

CRS is highly prevalent in patients with CF, accounts for significant morbidity and contributes to CF lung disease. Mutations of the CFTR gene are also seen with increased prevalence in non-CF CRS patients, suggesting some contribution to CRS pathophysiology. Reduced function of CFTR in CF patients negatively impacts sino-nasal mucociliary clearance due to an increase in the viscosity of sino-nasal epithelial lining fluid, and is associated with reduced ASL pH, increased baseline NPD and reduced nNO. Reduced nasal ASL pH has been causally linked to reduced airway innate immunity by virtue of detrimental effects on the function of antimicrobial proteins. Newborns with CF already manifest the physiological abnormalities of reduced CFTR function.

There is an increased prevalence of nasal polyps in CF patients of all ages. CF nasal polyps have a more neutrophilic appearance with fewer eosinophils and increased submucosal glandular elements compared with nasal polyps from non-CF patients.

CRS can be highly challenging to treat in CF patients owing to the increased mucus viscosity and decreased mucociliary clearance leading to chronic sinus infection and biofilm formation; the presence of distinctive sinus pathogens, including *S. aureus* (children), *P. aeruginosa* (children and adults) and unusual pathogens (e.g. *B. cepacia* or *A. xylosoxidans*), and the greater severity and poorer outcomes of CRS in CF relative to non-CF patients. Mainstays of medical treatment include isotonic saline irrigations and topical intranasal glucocorticoids, with some evidence that topical intranasal glucocorticoids reduce nasal polyp size. Mucolytics have received little attention as a treatment for CRS in CF and most evidence does not support their use for CF lung disease. Nasally nebulised dornase alfa following sinus surgery shows promise for treatment. There are studies supporting the use of topical antibiotics, including colistimethate sodium or tobramycin, administered as a saline irrigation or antral lavage in patients following sinus surgery when susceptible bacteria are cultured. Key components of CF sinus surgical management include extensive surgery to ensure that the maxillary, frontal, sphenoid and ethmoid sinuses are all widely opened with smoothing of bony overhangs to prevent mucus retention and bacterial recolonisation, post-operative meticulous daily nasal irrigations, and appropriate use of culture-directed topical antibiotics. There are no data yet on whether the CF-targeted therapies, including ivacaftor or ivacaftor combined with lumacaftor, have an impact on CF CRS.

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Infections in the nose and exacerbations of chronic respiratory disorders

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Respiratory viral infections and potentially bacterial infection/re-activation precipitate the vast majority of exacerbations of chronic respiratory disorders, such as asthma and COPD. The most commonly identified virus, human rhinovirus (hRV), mainly infects the upper respiratory epithelium causing mild symptoms associated with the common cold. Studies have demonstrated that, after nasal inoculation, hRV can infect bronchial epithelium, providing a mechanism by which hRV might trigger lower respiratory tract symptoms. The underlying mechanisms that ultimately lead to an exacerbation seem to be the result of various factors associated with the virus strain itself, the epigenetic and immunological patient profile (host antiviral defence), and the underlying disease status, as well as the sequence of immune and inflammatory responses induced after infection. The epithelium plays a pivotal role in viral adhesion and replication, while defective epithelial, innate and adaptive immune responses have been shown mainly in asthmatic subjects, more so in the presence of atopy. Exacerbations have long been associated with enhanced bacterial growth from respiratory cultures, and relationships between the nasopharyngeal/lung microbiome, acute infection and exacerbation, although still controversial, may provide novel targets for therapeutic interventions in the context of "united airways diseases".

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Chronic airway disorders, such as asthma and COPD, are a significant cause of morbidity and mortality worldwide, and their prevalence is predicted to increase in the future. Despite differences in underlying pathophysiology, both disorders present with chronic respiratory symptoms, as well as by acute worsening of symptoms [1].

Asthma is a heterogeneous, complex disease with clinical phenotypes that incorporate persistent symptoms and acute exacerbations, characterised by cough, wheezing and/or difficulty in

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breathing, associated with airflow obstruction [2]. It affects millions of people throughout their educational and working lives and puts a heavy cost/burden on productivity [3].

COPD patients experience varying levels of chronic symptoms, punctuated by periods of sustained acute deterioration during which they experience increases in dyspnoea, cough with sputum production and purulence, which are associated with increased airflow limitation and dynamic hyperinflation, which can result in respiratory failure [4]. COPD is predicted to be the fourth leading cause of mortality by 2030 [5].

Although airway exacerbations are universally accepted as the major cause of morbidity and healthcare costs in these respective diseases [6, 7], objective criteria for defining such events are lacking, and it is sometimes difficult to differentiate an exacerbation from poor disease control [8]. It is accepted for both asthma and COPD that an exacerbation is an event in the natural course of the disease characterised by an increase in the patient's baseline symptoms that are beyond the day-to-day variations [6, 9]. Severe exacerbations have been defined as events requiring urgent action to prevent serious outcomes, such as hospitalisation or death, whereas moderate exacerbations are troublesome to the patient or events that prompt a change in treatment, and are outside the patient's usual range of day-to-day asthma variation, although thresholds from loss of control are often indistinguishable [10]. Whether "mild exacerbations" exist is questionable because such events can be indistinguishable from loss of control.

Although existing evidence suggests that asthma and COPD exacerbations are probably a result of synergistic and/or additive interactions among several factors, such as allergen exposure, air pollution, temperature variation, medication adherence and psychological stress, it is well established that respiratory viral infections and potentially bacterial infection/re-activation precipitate the vast majority of such exacerbations [11, 12]. With the advent of powerful molecular detection methods and detailed analysis of epidemiological data, our understanding of the implication of viral infections in airway exacerbations has increased [13]. Occasionally, particularly in young children, common colds are unique precipitants of wheezing and associated symptoms. Airway viral infections frequently cause exacerbation of asthma. It is well established that the optimal temperature for human rhinovirus (hRV) proliferation is 33°C, which represents the mean nasal temperature. Subsequent studies demonstrating that, following nasal inoculation, hRVs can infect bronchial epithelium, and moreover that experimental hRV infection in subjects with asthma precipitates acute exacerbation, have provided direct evidence of a causative role for hRVs [14, 15].

More recently, infections have also been acknowledged as major determinants of COPD exacerbations [16]. At present, there are few available therapies that target respiratory infections either nonspecifically or specifically by virus type. A growing body of evidence suggests that reversing deficient IFN production in asthmatic patients could be a novel target for therapeutic intervention in the context of virus-induced asthma exacerbations. In addition, despite overwhelming interest and activity in developing viral inhibitors and viral vaccines, no antivirals have specifically been trialled in models of asthma exacerbations [17]. Highlighting underlying pathogenic pathways of chronic lung disease exacerbations could enable us to design and select optimal therapeutic strategies.

This chapter presents current evidence on the associations between upper and lower respiratory tract infections and exacerbations of established asthma and COPD.

Epidemiology of virus-induced exacerbations

The development of sensitive diagnostic polymerase chain reaction-based techniques for the detection of the most prevalent respiratory viruses has permitted confirmation of the well-established clinical experience of acute asthma and COPD worsening following a common cold. Paediatric studies were able to identify respiratory viruses in 62–95% of wheezing children (with more cases reporting a prevalence of >80%) in both community and hospital settings, resulting also in reduced lung function [18]. In adults, lower estimates were recorded for asthma and COPD exacerbations attributed to viral infections (45–80%), probably because of pragmatic differences in the prevalence of virus-induced exacerbations or due to the fact that adults shed less infective virus [19]. This knowledge was summarised in a systematic review of the microbial epidemiology of acute asthma in children and adults, as well as the prevalence of specific agents in asthma exacerbations [20].

With regard to asthma, hRVs are the most frequently detected viruses (60% of cases of asthma exacerbation) in both children and adults [21]. Interestingly, studies have suggested that hRV, besides being the most prevalent, is also the only virus significantly associated with exacerbations in children (OR 6.8, 95% CI 3.2–14.5) [22]. Usually, hRV infects the upper respiratory epithelium and for most people causes only a relatively mild illness (*i.e.* a common cold). Remarkably, >50% of bronchial epithelial biopsies collected from patients with stable asthma and from healthy controls were found to be hRV-positive [23]. hRV-A and hRV-B have long been recognised as playing a significant role in exacerbations [24, 25], whereas recent studies have identified the novel hRV-C as being strongly associated, especially with severe exacerbations [26]. Such an association might be attributed either to genetic susceptibility, as cadherin-related family member 3 (CDHR3) that mediates hRV-C binding and replication is hyperexpressed [27], or due to ineffective specific immune responses (IgG_1 species-specific titres) in certain asthmatic individuals [28].

In terms of seasonality, the peak of severe asthma exacerbations in children occurs shortly after their return to school following breaks, and 1 week later in adults, and this coincides with peaks in hRV infections in the autumn and, to a lesser extent, in the spring [29, 30]. Other respiratory viruses responsible for exacerbations display different seasonal variations: respiratory syncytial virus (RSV) and influenza virus have been associated with increased asthma exacerbations during the winter months [31]. The 2009 H1N1 influenza A virus pandemic brought about a number of studies highlighting asthma as an important comorbidity in those infected, and was associated with increased disease severity, a higher risk of hospitalisation, the need for intensive care and overall mortality [32]. Among the most recently identified viruses, human metapneumovirus (hMPV) has been associated with wheezing episodes, mostly in younger children, whereas human bocavirus (hBoV) is found in ~5% of asthma exacerbations [33, 34].

Mycoplasma pneumoniae and *Chlamydophila pneumoniae* are found more frequently in the airways of patients with asthma in comparison with healthy controls; however, their role in exacerbations is less clear and is hampered by methodological problems in their kinetics and identification [35]. In the majority of exacerbation studies looking for a wide array of pathogens, the relative proportion of atypical bacteria detected is low.

With respect to COPD, most exacerbations are associated with respiratory infections, and historically bacterial infections were considered the main infective cause, with a prevalence ranging from 26% to 81%, as also reflected in the high rates of antibiotic use during exacerbations [36]. A systematic review of 19 studies including a total of 1782 patients highlighted that hRVs/enteroviruses, RSV and influenza viruses were the most prevalent viruses detected, with lower detection rates for parainfluenzaviruses and coronaviruses. Adenovirus, hMPV and hBoVs appear not to be associated with COPD exacerbations [37]. Case–control studies have demonstrated higher virus detection rates, while viral kinetics and loads in COPD exacerbations are indicative of a causal relationship [38].

Pathogenesis

In respiratory viral infections, the compromise of respiratory equilibrium that ultimately leads to exacerbation seems to be the result of various factors associated with the virus strain itself, the epigenetic and immunological patient profile (host antiviral defence), and the underlying disease status, but also with the sequence of immune and inflammatory responses induced after infection. An integrated response, including the respiratory, immune and nervous system, aims at efficient clearance of the virus.

The majority of current *in vitro* and *in vivo* studies focus on the effects of hRVs, because this is the virus type detected most commonly in asthma exacerbations. The major and minor groups of hRVs bind to intercellular adhesion molecule (ICAM)-1 (90% of strains) and low-density lipoprotein receptors, respectively, on the respiratory epithelium and generate either double- (ds) or single-stranded (ss) viral RNA in their host cells. Bronchial epithelial cells (BECs) serve as the major host cell for viral replication, although other cell types such as smooth muscle cells, fibroblasts and alveolar macrophages have also been reported [14]. Subsequently, innate immune responses are triggered by binding to pattern recognition receptors (PRRs; proteins expressed in cells of innate immunity identifying pathogens), including Toll-like receptor 3 (TLR3) and the family of RNA helicases, *i.e.* retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) [39]. TLR3 recognises viral dsRNA and polyinosinic–polycytidylic acid (poly(I:C)), a synthetic analogue of dsRNA, in the endosome and initiates signalling through Toll/IL-1R domain-containing adaptor-inducing IFN-β (TRIF; also known as TICAM-1), while TLR7/8 recognises ssRNA [40]. The virus–PRR interaction initiates cascades that produce type I IFNs (IFN-α/β), type III IFNs (IFN-λ) and a variety of pro-inflammatory cytokines, chemokines and costimulatory molecules. Subsequently, recruitment and activation of neutrophils, eosinophils, $CD4^+$ cells, $CD8^+$ cells and mast cells through increased mRNA expression and translation of IL-6, IL-8, IL-16, eotaxin, IFN-γ-induced protein 10 (IP-10)/CXCL10 and CCL5/RANTES (regulated on activation, normal T-cell expressed and secreted) has been documented in the airway mucosa, potentiating inflammation and leading to an exacerbation [41]. IFNs bind to the respective receptors expressed on cells infected with a virus, inducing apoptosis to prevent virus spreading, while an array of IFN-responsive gene products that prevent virus proliferation are expressed [42]. Therefore, a robust IFN response is central to effective antiviral responses and resolution of virus infection [43].

In addition, hRVs are also able to pass into the bloodstream more frequently during acute and severe asthma exacerbations, causing viraemia [44].

Epithelial cells

The extent of epithelial cell destruction varies according to the type of virus. Influenza virus has been shown to cause extensive epithelial necrosis, whereas hRVs usually cause little or only patchy epithelial damage. Early on, *in vitro* models demonstrated that hRV infection may modulate epithelial responses by delaying epithelial repair [45], which has also been confirmed in an *ex vivo* model of hRV infection in cells from asthmatic children [46]. Moreover, in the presence of an atopic environment, hRV-induced epithelial responses are altered, reducing viral clearance and promoting cytotoxicity [47]. hRV infections have also been shown to promote airway remodelling by inducing angiogenesis, mediated through vascular endothelial growth factor (VEGF), an effect also enhanced in the presence of atopy [48]. Similar responses were also observed for other pro-fibrotic factors, such as transforming growth factor (TGF)-β [47] and fibroblast growth factor 2 [49]. Confirmation of the aforementioned data derives from studies reporting that hRV infection of cultured epithelial cells upregulates amphiregulin (a member of the epidermal growth factor family), activin (a member of the TGF-β family) and VEGF [50].

In addition, hRV infection induces increased mucin production in primary human BECs and mucous cell metaplasia *in vivo*, either mediated through a TLR3 or an NF-κB and epidermal growth factor receptor (EGFR) signalling pathway [51, 52].

Other cell types, including B-cells

Experimental human models of virus-induced exacerbations have revealed an increase in epithelial eosinophils in submucosal lymphocytes and most importantly in neutrophils and CD68$^+$ macrophages, with the latter being correlated with decreased lung function [24, 53]. Moreover, *in vitro* models have shown that hRVs are able to infect human macrophages [54], T-cells [55] and Ramos cells (a human B-lymphocyte cell line) [56]. However, only a limited proportion of cells are positive for viral replication. It has been shown that, during viral infection, polarisation of macrophages occurs towards the M1 phenotype (pro-inflammatory), further contributing to inflammation [57]. Innate activation of monocytes upon viral infection and infiltration of inflammatory cells might influence immune responses to hRVs, further contributing to the processes of asthma exacerbations [58].

More recently, it has been shown that hRVs can enter and replicate in B-lymphocytes and induce proliferation, while the newly formed virions can further infect HeLa cells [59]. The production of several inflammatory cytokines from peripheral mononuclear cells has also been demonstrated, possibly contributing to asthma exacerbations [59, 60].

In terms of an adaptive immune response to hRV, an HLA-DR4-restricted CD4-specific epitope, a region that is conserved across hRV groups A, B and C, has recently been identified, indicating that effector/memory cells are activated in response to common epitopes displayed by infecting hRVs on re-infection [61]. Moreover, hRVs induce maturation of dendritic cells on infection, which subsequently stimulates CD4 and CD8 proliferation, resulting in IFN-γ production [62]. These results indicate that CD4$^+$ cells induced by one hRV type can respond to other strains, allowing a rapid response to hRV re-infection, and subsequently promote Th2 cytokines, potentially exacerbating an ongoing allergic inflammation.

Innate lymphoid cells

ILCs are a newly characterised effector cell population of innate immunity. They can either initiate or augment the Th2-mediated response by recruitment of eosinophils, neutrophils and macrophages [63]. As has been shown in other circumstances, injury to epithelial surfaces triggers the release of a variety of pro-inflammatory and Th2-promoting cytokines, the latter including IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) [64]. *In vitro* infection of BECs with hRV or RSV, or exposure to dsRNA in order to simulate infection, induces production of TSLP [65], while increases in IL-25 levels, mainly in asthmatic subjects, have also been demonstrated [66, 67]. Subsequently, Th2 cytokine release, such as IL-5 and IL-13 from ILCs, occurs, further promoting Th2 responses and the induction of mucus production. IL-33, a Th2-promoting cytokine and a “damage-associated” molecule or alarmin [68], has also been induced by BECs following hRV infection, more so in asthmatic subjects, and IL-33 from infected BECs was shown to strongly induce IL-5 and IL-13 from human ILCs [69]. Importantly, in an hRV-induced exacerbation model, IL-4, IL-5 and IL-13 were induced *in vivo* in subjects with asthma but not in normal controls, while levels of these cytokines correlated significantly with exacerbation severity [69]. These results provide further evidence that hRV can induce a Th2 cytokine response that could result in an exaggerated allergic immune response and thereby cause exacerbations in asthmatic individuals.

Cytokines

hRV infection activates inflammatory pathways by recruiting and activating mainly neutrophils and to a lesser extent eosinophils, $CD4^+$ cells, $CD8^+$ cells and mast cells through increased mRNA expression and translation of pro-inflammatory cytokines and chemokines [2].

Defective production of IL-15, a cytokine implicated in innate and acquired antiviral immunity, was noted in asthmatic subjects following experimental hRV infection, while its induction has been inversely related to airway hyperresponsiveness (AHR) and virus load in animal models [70].

Recently, it was reported that IL-17A might play an important role in neutrophilic inflammation, which is characteristic of such exacerbations, through increased production of neutrophil chemoattractants. Specifically, stimulation of human BEAS-2B cells with a mimic of viral dsDNA showed that IL-17A might be associated with the pathogenesis of viral infection-triggered exacerbations by promoting the release of CXCL1 (GRO1 oncogene) and CXCL8 (IL-8) (neutrophil chemoattractants) from BECs [71]. Importantly, IL-17A has been shown to demonstrate antiviral immune responses by inhibiting hRV replication, while hRV infections in human BECs inhibit IL-17A responses [55]. Moreover, in an experimental model, hRV-infected Tbet (a transcription factor that orchestrates Th1 differentiation)-deficient mice developed Th2 and Th17 responses, which were associated with impaired hRV-specific antibody production (IgG_2), airway eosinophilia and enhanced mucus hypersecretion [72]. The functions of epithelium-derived cytokines and chemokines are described in table 1.

It is well known that steroids are partially ineffective in virus-induced exacerbation. It has been shown that hRV-16 infection impairs dexamethasone-dependent anti-inflammatory activities, including inhibition of: 1) IL-1β-induced CXCL8 release, and 2) binding of glucocorticosteroid receptor to G-elements in the promoter region of responsive genes, through activation of the NF-κB pathway. These observations provide insights on the glucocorticosteroid resistance in virus-induced exacerbations [73].

Moreover, viruses generate systemic as well as neural responses, further inducing inflammation and AHR.

Table 1. Major functions of epithelium-derived cytokines and chemokines affecting chronic lung disease manifestations

Cytokine/chemokine	Function
IL-6	Pleiotropic cytokine that can be produced by many cell types in response to a wide array of inflammatory stimuli and cytokines; IL-6 has both pro-inflammatory and anti-inflammatory properties; a plausible mediator of airway dysfunction in asthma; increased serum and bronchoalveolar lavage levels during exacerbations of COPD
IL-8	Chemoattractant for neutrophils, NKT-cells (cells of the innate immune system whose principal role is to kill virus-infected cells), T-cells, basophils and eosinophils; angiogenesis
IL-15	Secreted by mononuclear phagocytes (and some other cells) following infection by virus(es); it induces cell proliferation of NKT-cells
IL-16	Induction of pro-inflammatory cytokines, chemokines and metalloproteases; recruitment and activation of neutrophils
IL-17B, -17C, -17D	Induction of antimicrobial peptides, pro-inflammatory cytokines, chemokines and metalloproteases
IL-18	Induction of IFN-γ in the presence of IL-12; enhancement of NKT-cell cytotoxicity, promoting Th1 or Th2 cell responses depending on the cytokine milieu
IL-25	Induction of Th2 responses and inhibition of both Th1 and Th17 cell responses; induction of IgE, IgG_1, IL-4, IL-5, IL-13 and IL-9 production
IL-33	Transcriptional repressor activity; induction of Th2-type inflammation on mucosal tissues; maturation factor for bone marrow-derived dendritic cells accompanied by the release of pro-inflammatory cytokines; enhanced integrin expression in basophils and eosinophils; inducer of ILCs
TGF-β	Induction of epithelial and endothelial to mesenchymal transition; balance of pro-inflammatory and anti-inflammatory effects by decreasing the cellular growth of almost all immune cell precursors; regulation of the differentiation of several Th cell subsets and induction of T-regulatory cells; suppression of IFN responses; immune tolerance
TSLP	Acts on dendritic cells, monocytes, $CD4^+$ T-cells, mast cells and B-cells, promoting development of the Th2 inflammatory response, often in cooperation with IL-25, IL-33 and other cytokines
RANTES (CCL5)	A chemotactic cytokine or chemokine; chemotactic for T-cells, eosinophils and basophils, and plays an active role in recruiting leukocytes into inflammatory sites
CCL2 (MCP-1)	Belongs to the CC chemokine family; recruits monocytes, memory T-cells and dendritic cells to the sites of inflammation produced by either tissue injury or infection
CCL8 (MCP-2)	Chemotactic for and activates many different immune cells, including mast cells, eosinophils and basophils (which are implicated in allergic responses), and monocytes, T-cells and NKT-cells involved in the inflammatory response
CCL17 (TARC)	Belongs to the CC chemokine family; role in the induction of chemotaxis in T-cells; elicits its effects by interacting with the chemokine receptor CCR4
CCL20 (MIP-3α)	Belongs to the CC chemokine family; strongly chemotactic for lymphocytes and weakly attracts neutrophils
CCL22 (MDC)	Produced by dendritic cells and macrophages and elicits its effects on its target cells by interacting with cell surface chemokine receptors such as CCR4
CXCL10 (IP-10)	Secreted by several cell types in response to IFN-γ; it is a chemoattractant for monocytes/macrophages, T-cells, NKT-cells and dendritic cells

Continued

Table 1. Continued

Cytokine/chemokine	Function
CXCL9	A T-cell chemoattractant, which is induced by IFN-γ
CXCL13	Belongs to the CXC chemokine family; selectively chemotactic for B-cells belonging to both the B-1 and B-2 subsets, and elicits its effects by interacting with the chemokine receptor CXCR5
IFNs	Signalling proteins produced by host cells in response to the presence of several pathogens, such as viruses, bacteria, parasites and also tumour cells

TGF: transforming growth factor; TSLP: thymic stromal lymphopoietin; RANTES: regulated on activation, normal T-cell expressed and secreted; MCP-1/2: monocyte chemotactic protein 1/2; TARC: thymus and activation-regulated chemokine; MIP-3α: macrophage inflammatory protein 3α; MDC: macrophage-derived chemokine; IP-10: IFN-γ-induced protein 10.

Interferons

Type I IFNs (α/β) and type III IFNs, including IFN-λ1 and IFN-λ2/3, are important components of the innate immune response, inducing an antiviral state in infected and nearby cells *via* induction of apoptosis and proteins with direct antiviral activity [74, 75]. Viral infections induce IFNs; however, IFN-λ seems to be the most abundant and sustained IFN subtype in the lungs [76].

In vitro studies are indicative of a defective type I and mostly type III IFN responses resulting in a deficient adaptive Th1 cell response [77], which can subsequently lead to increased viral replication in asthmatic patients; such responses have been strongly inversely associated with the severity of clinical illness, diminished lung function and increased AHR [78]. Defects in type I or type III IFNs may be due to antagonism of IFN receptor signalling by the suppressor of cytokine signalling 1, which can be induced by IL-13 as well as by virus infection itself [79]. Nevertheless, other *in vivo* studies have not confirmed these associations [80], although differences might be attributed to virus load differences in the *in vivo* model.

Ex vivo models of hRV-infected bronchoalveolar lavage cells were also indicative of a defective induction of type I IFN (IFN-α2, total IFN-α and IFN-β) only in asthmatic subjects. These deficient IFN responses were positively associated with measures of allergy and AHR [81]. In parallel, studies of experimental infection of BECs derived from asthmatic children also resulted in reduced IFN-β and increased inflammatory cytokine production [46]. Th2-biased upper airway inflammation is associated with an impaired response to viral infection with herpes simplex virus type 1 [82]. Moreover, increased sputum IFN-γ mRNA expression was observed during asthma exacerbations [83], while in a clinical setting of preschool children, increased levels of IFN-α induction were observed in the course of virus-associated asthma exacerbation, indicating a hyperactive immune response [84]. Emerging mechanisms involved in exacerbations of chronic lung diseases are depicted in figure 1.

IFN deficiency is a biologically plausible mechanism underlying the observed increased severity of virus-induced exacerbations, but it has not been universally demonstrated. Although inhaled IFN-β supplementation to prevent virus-induced worsening of asthma in mild asthmatic subjects has failed to show a positive effect, subanalysis in a group with a severe asthma phenotype showed a significant protective effect [85]. It is possible that differences in disease characteristics and/or the population included in the studies, as well as methodological

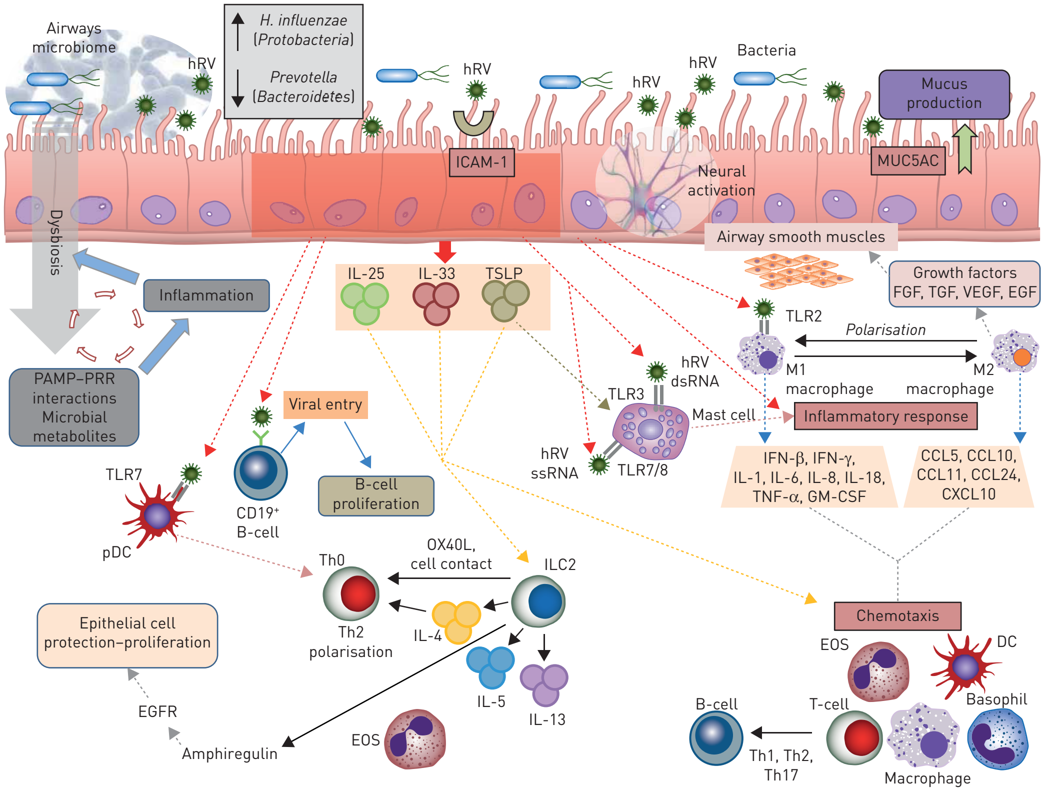
Airways microbiome
hRV
↑ H. influenzae (Protobacteria)
↓ Prevotella (Bacteroidetes)
hRV
hRV
hRV
Bacteria
Mucus production
ICAM-1
MUC5AC
Neural activation
Dysbiosis
Airway smooth muscles
Inflammation
IL-25
IL-33
TSLP
Growth factors FGF, TGF, VEGF, EGF
TLR2
Polarisation
M1 macrophage
M2 macrophage
PAMP–PRR interactions Microbial metabolites
Viral entry
hRV dsRNA
TLR3
Mast cell
Inflammatory response
hRV ssRNA
TLR7/8
IFN-β, IFN-γ, IL-1, IL-6, IL-8, IL-18, TNF-α, GM-CSF
CCL5, CCL10, CCL11, CCL24, CXCL10
TLR7
CD19+ B-cell
B-cell proliferation
pDC
OX40L, cell contact
Th0
ILC2
Th2 polarisation
IL-4
Chemotaxis
EOS
DC
Epithelial cell protection–proliferation
IL-5
IL-13
Basophil
B-cell
T-cell
EGFR
EOS
Amphiregulin
Th1, Th2, Th17
Macrophage

Figure 1. Emerging mechanisms in virus-induced exacerbations of chronic lung diseases. Human rhinoviruses (hRVs) interact with pattern recognition receptors (PRRs), inducing epithelial injury, which in turn induces Th2-promoting cytokine release, including IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). Subsequently, recruitment and activation of ILC2 cells amplifies inflammation *via* IL-5 and IL-13 release. Macrophages can be activated indirectly though TSLP. IL-17 enhances neutrophilic inflammation and has antiviral immune responses. Viral binding leads macrophages to M2 polarisation, inducing angiogenesis and fibrosis, enhancement of inflammation and reduction of antiviral activity of M1-type macrophages. hRVs can enter and replicate in B-cells inducing proliferation. Airway microbiome dysbiosis provokes airway inflammation *via* pathogen-associated molecular pattern (PAMP)–PRR interactions and microbial metabolite signalling to epithelial cells, perpetuating airway inflammation. ICAM-1: intercellular adhesion molecule 1; MUC5AC: mucin 5AC; FGF: fibroblast growth factor; TGF: transforming growth factor; VEGF: vascular endothelial growth factor; EGF(R): epidermal growth factor (receptor); TLR: Toll-like receptor; ds/ssRNA: double/single-stranded RNA; TNF: tumour necrosis factor; GM-CSF: granulocyte–macrophage colony-stimulating factor; (p)DC: (plasmacytoid) dendritic cell; OX40L: OX40 ligand; EOS: eosinophil.

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differences, could account for such discrepancies; however, more studies are needed to clarify this point.

Interaction of viral infections with atopy

Despite the importance of viral infections in asthma exacerbation pathogenesis, a combination of interacting factors is likely to be involved. Studies performed during the last decade have emphasised the importance of atopy and allergic inflammation in the induction and perpetuation of virus-induced respiratory diseases [86]. The issue of whether atopy alone could account for both symptoms and exacerbations of asthma is still being debated.

hRV-induced epithelial cytotoxicity could increase the penetration and effects of allergens, leading to further induction of inflammation [47]. More recently it has been shown that hRV-induced asthma exacerbations are more prevalent in the presence of high IgE titres to relevant allergens, indicating the important role of the host's atopic status [87]. Using house dust mite allergen and the viral mimic poly(I:C) (viral mimetic/TLR3 agonist) in a mouse model, induction of neutrophilic inflammation was observed that was insensitive to oral steroid therapy, thus providing a mechanism of severe virus-induced exacerbation [88].

In clinical settings, allergens and respiratory viruses act synergistically in the expression of asthma symptoms in adults and children [89]. Notably, the sharp increase in emergency department visits for virus-induced asthma exacerbations in September has been postulated to be affected by aeroallergen concentrations on host responses [90]. When routine nasal secretion samples were obtained during hRV high-prevalence seasons, allergic sensitisation was associated with prolonged and more severe exacerbations in asthmatic children, although viral detection rates did not differ between groups [91]. Moreover, in children, hRV-induced IFN-λ and IFN-β induction correlated inversely with airway Th2 markers and IgE levels [92]. Recent studies are indicative of an exaggerated IL-25 response in asthmatic subjects further activating Th2-driven inflammation during hRV-induced asthma exacerbations, and more so in the presence of atopy [66].

From another perspective, studies using major histocompatibility complex class II tetramers demonstrated that circulating allergen-specific T-cells increased up to ~10-fold during the allergy season [93]. It has been postulated that the presence of an ongoing T-cell and IgE-mediated inflammatory response to allergens acts synergistically with hRV-induced Th2 responses, leading to asthma exacerbation in susceptible individuals. This concept is consistent with the effectiveness of omalizumab in preventing asthma exacerbations by restoration of antiviral immunity and possibly by blocking the synergistic effect of hRV infection and allergy, although the exact mechanism remains to be elucidated [94].

Bacterial infections and asthma exacerbations

Most of the studies investigating the role of *M. pneumoniae* and *C. pneumoniae* (six studies in children) in acute asthma symptoms are indicative of a positive association, with a reported prevalence of 5–30% in wheezing episodes and/or acute asthma exacerbations [35]. Biscardi *et al.* [95] found that *M. pneumoniae* was present in 20% of exacerbations in asthmatic children requiring hospitalisation and in 50% of children experiencing their first asthmatic attack. Nevertheless, *M. pneumoniae* and *C. pneumoniae* infections may also be accompanied by wheezing in children considered not to have asthma; *M. pneumoniae* infection has been reported in 25–40% and in 35% of the general paediatric population presenting with wheezing and pneumonia, respectively [96, 97]. It has been proposed that *M. pneumoniae* infections may aggravate asthma by inducing mucin (MUC5AC, the major airway mucin) expression, possibly *via* TLR2 or by signal transducer and activator of transcription 6 (STAT6)–STAT3 and EGFR signalling pathways activation [98, 99].

There are still unresolved issues with respect to both microorganism identification and study design before an aetiological association can be firmly established [35]. Interestingly, in a prospective study, acute wheezy episodes in preschoolers were significantly associated with *Haemophilus influenzae* and *Moraxella catarrhalis*, but not with *Streptococcus pneumoniae* [100].

In a prospective paediatric study, it was shown that when hRVs infections were associated with increased detection rates of *S. pneumoniae* and *M. catarrhalis*, an increased risk for moderate asthma exacerbation was noted [101]. Moreover, detection of *Streptococcus* spp. with concurrent hRV-C infection early in life increases the risk for subsequent childhood wheezing, indicating the importance of the nasopharyngeal microbiome in the first years of life [102]. From another perspective, early antibiotic use was associated with increased risk of subsequent severe asthma exacerbation and hospitalisation following virus-induced infection [103].

COPD and viral infections

Viruses, particularly RSV and hRVs, are increasingly thought to be major triggers in COPD exacerbations, with a detection rate of 22–65% [104, 105]. Other viruses such as hMPV and hBoV are implicated less frequently in COPD exacerbations [34, 106], while increased severity COPD exacerbation outcomes were recorded with respect to influenza virus infections [107]. Surprisingly few *in vitro* studies and studies of naturally occurring exacerbations compare cell responses from COPD patients following a viral infection with those from healthy control subjects.

It is well established that smoking damages mucociliary clearance and that the hRV-binding receptor ICAM-1 is upregulated in COPD BECs and in patients with chronic airflow limitation [108–110]. Most importantly, alveolar macrophages demonstrate defensive impairments, as suggested by reduced bacterial phagocytosis and impaired induction of IL-8 and tumour necrosis factor [111].

Epithelial cells also act as a key element in COPD infections, in particular *via* the production of IL-33–high progenitor cells in the lung, which, under the pressure of danger signals, result in IL-13 induction and subsequent mucous production. This could lead to epithelial reprogramming, which may drive disease even the absence of continued exposure to noxious agents, such as smoke [112].

In experimental hRV infections in COPD models, increased numbers of neutrophils, macrophages and lymphocytes are found [113], while pro-inflammatory cytokine responses are less clear [114, 115].

Moreover, mucous impaction and hyperconcentration play a pivotal role in COPD, and viruses such as RSV have been shown to increase mucin secretion *in vitro*, while the patchy nature of mucous clearance is closely linked to exacerbation [51].

It is still debated whether innate immune responses are defective in COPD patients, with studies presenting conflicting results. In mouse models of COPD, hRV infection induced inflammation and deficient IFN responses and viral clearance compared with controls [116]. Moreover, in human models, impaired IFN-β production and neutrophilic inflammation have been demonstrated in COPD subjects following experimental hRV-16 infection, and this was closely associated with an increased severity of hRV infection in COPD patients [117]. By contrast, IFN responses have been shown to be increased in cigarette smoke- and influenza-exposed mice and in hRV-exposed epithelial cells derived from COPD patients [76, 118], although other studies failed to produce any alterations in IFN production following infection [113]. Surprisingly, although several antiviral molecules are upregulated mainly in the epithelial cells of COPD patients following *ex vivo* infection, such as IFN-λ, CXCL8/IL-8, CXCL10/IP-10, IL-6, ICAM-1, NADPH oxidase 1, dual oxidase 1/2, STAT1 and STAT2, proliferation of hRV was more vigorous in the COPD patient-derived cells, indicating impaired antiviral mediators [119].

Viral and bacterial infections

Among the microorganisms involved in infectious exacerbations, the most common bacterium was *H. influenzae*, followed by *S. pneumoniae* and *M. catarrhalis* [120]. However, in patients with severe COPD who receive more antibiotic treatments or experience more severe exacerbations, *Pseudomonas aeruginosa* and *Enterobacteriaceae* are more frequently observed [120]. Interestingly, some species of bacteria are typical COPD pathogens and contribute to exacerbations, whereas certain microbiome members seem to contribute to functional homeostasis in COPD airways.

Interestingly, up to 25% of patients may present bacterial and viral co-infection [121]. It has been suggested that viral, especially hRV, infections precipitate secondary bacterial infections, altering the respiratory microbiome, and such changes correlated with more severe exacerbations [122, 123]. COPD exacerbations in patients with both hRV and *H. influenzae* infection presented increased viral loads [124], while dual infection (viral and bacterial) was associated with more marked pulmonary function impairment and prolonged duration of hospitalisation in hospitalised COPD individuals [125]. In terms of underlying pathogenic mechanisms, viral infections, and particularly hRV infections, have been shown to induce changes in the sputum microbiome and facilitate subsequent bacterial infection [126]. Moreover, viral infections promote bacterial adhesion and invasion through either damaged epithelium, or delayed bacterial clearance *via* reduced neutrophilic recruitment and activation [127]. Impaired innate bacterial responses through reduced macrophage cytokine release and/or reduced antimicrobial product levels have been also been implicated [122, 128].

Respiratory tract microbiome and exacerbations

Although it was Joshua Lederberg who in 2001 popularised the term microbiome [129], the idea that humans coexist with microorganisms is not new. In 1681, Antoine van Leeuwenhoek described "animalcules" in his own stool, in a letter to Robert Hooke of the Royal Society [130]. Although there is not a universally accepted definition, the term microbiome (micro+biome) refers to the sum of all microorganisms (microbiota), their genomes (metagenomes), their activity and interactions. The term includes all members of an ecological community of commensal (established pattern), opportunistic (random pattern), symbiotic and "potentially" pathogenic microorganisms that share our body space [130].

The human lung was long considered to be sterile in the absence of a symptomatic active disease and as a result it was not included in the first Human Microbiome Project [131]. Today, it is widely accepted that there is a lung microbiome, although the interactions with the pulmonary immune system and what constitutes a "distinct" lung microbiome remain a matter of debate. Charlson *et al.* [132] found that the respiratory tract harbours homogeneous microbiota that decrease in biomass from upper to lower tract and that the healthy lung does not contain a consistent distinct microbiome but low levels of bacterial sequences that are largely indistinguishable from upper respiratory flora. In line with these results, Dickson *et al.* [133] found that species richness decreased with increasing distance from the "source" community of the upper respiratory tract. These results suggest that the lung microbiome in health is more influenced by microbial immigration and elimination (the adapted island model) than by effects of local growth conditions on bacterial reproduction rates, which are more determinant in advanced lung diseases [133].

Recently, data are beginning to emerge with respect to asthma, the phylum *Proteobacteria* and potential bacterial dysbiosis patterns [134–137]. Site-dependent microbial community differences between samples obtained from the nose, the oropharynx and the left upper lobe of healthy, asthmatic and COPD patients were identified by Hilty *et al.* [134]. Pathogenic members of the phylum *Proteobacteria*, in particular *Haemophilus* spp., were more frequent in asthmatic bronchi of adults or in patients with COPD than in controls. The same pattern was observed in children. Conversely, *Prevotella* spp., of the phylum *Bacteroidetes*, were more prevalent in controls than in adult or child asthma/COPD patients [134]. Notably, all asthmatic subjects were on corticosteroid therapies (inhaled or oral). However, lower airway samples were clustered better in the presence of a respiratory disease, suggesting that the asthmatic (and/or COPD) phenotype influences the "fixation" of a distinct bacterial profile in the lung, and *vice versa*. In the Bronchoscopic Exploratory Research Study of Biomarkers in Corticosteroid-refractory Asthma (BOBCAT) study, specific microbiota of the phyla *Bacteroidetes* and *Firmicutes* found in bronchial brushings of patients with severe asthma were strongly correlated with body mass index [137]. Moreover, lower Asthma Control Questionnaire scores were associated with greater relative abundance of *Proteobacteria* (*e.g. Enterobacteriaceae*, *Neisseriaceae* and *Pasteurellaceae*). Importantly, different microbiota, even within the same bacterial taxon (phylum, family or even genus) were implicated in different features of asthma including Th17-related or non-type 2 airway inflammation and potential modulation of treatment responses (*e.g.* corticosteroids). Nevertheless, significant intra- and inter-subject heterogeneity was still present with variations impacted by factors such as disease stage and inhaled medications.

Exacerbations have long been associated with viral infections and bacterial growth from respiratory cultures as stated previously, but the borderline relationships between the nasopharyngeal/lung microbiome, acute infection and exacerbation remain controversial [138]. To date, alterations in the lung microbiome acting either as a cause or an effect have been associated mostly with CF and COPD exacerbations. With respect to asthma, no culture-independent studies have included respiratory specimens acquired from asthmatic subjects in the context of an exacerbation, although it has been shown that the microbiota detected in asthmatic airways at baseline is consistently and significantly distinct from that of control subjects [139]. From another perspective, it has been shown that AHR, which is increased during exacerbations, is strongly associated with increased respiratory *Proteobacteria* abundance, while clinical improvement was demonstrated following clarithromycin treatment, suggesting a close link of microbiome composition and risk for asthma exacerbation [135]. More than 100 phylotypes, including families within the phylum *Proteobacteria*, that are known to be potentially pathogenic or whose functions can contribute towards the pathophysiology of asthma were correlated with AHR, suggesting possible functional microbial–host interactions. There are numerous studies that demonstrate that the lung microbiota is different in COPD patients [123, 140–146]. A plethora of bacterial taxa have been identified as part of a "core" lower airway microbiome from COPD patients experiencing severe exacerbations, suggesting that the pathogenesis of exacerbations could involve a multimicrobial process [140]. Moreover, COPD patients with a richer bacterial community, mostly populated by commensal nonpathogenic bacteria, received ventilatory support for a shorter period of time [140]. However, changes in overall bacterial community diversity (increasing or decreasing) during COPD are not necessarily linearly correlated with progression of disease. Community diversity may fluctuate based on the microbiota dynamics, such as the emergence of a pathogen that numerically dominates the site or impaired clearance of microaspirated anaerobes [146]. Whether patients with a "frequent exacerbator" phenotype possess specific or greater alterations in their airway microbiome that predispose them to recurrent exacerbations compared with nonfrequent exacerbators needs to be determined [147].

In contrast to the lung microbiome, the presence of a well-defined nasopharyngeal microbiome has been established [102, 148–151]. The five most prevalent phyla present are *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Fusobacteria*. The nasopharyngeal microbiome is governed by different dynamics (*i.e.* different biological equilibria) than the oral cavity microbiome [148, 152–154]. A "core" bacterial microbiome has been described composed of *H. influenzae* and *Moraxella*, *Enhydrobacter*, *Streptococcus*, *Dolosigranulum* and *Corynebacterium* spp. [148]. The presence of potential pathogenic bacterial species as part of a "healthy" nasopharyngeal microbiome has been also described elsewhere [102, 151] and challenges our understanding of the pathogenicity of these strains. However, the nasopharyngeal microbiota profiles can be affected by season [148, 155], history of acute sinusitis [150], hRV infections [156, 157], allergic rhinitis [155], age [102, 149, 151] and environmental factors such as day-care, antibiotics and siblings [102]. Environmental factors such as exposure to farming have also been shown to potentially "modify" the correlation of specific bacterial species and asthma; DEPNER *et al.* [158] demonstrated that a specific operational taxonomic unit from the genus *Moraxella* was positively associated with asthma presence only in children not exposed to farming. Asthma was also correlated with lower bacterial richness (equally in farm and nonfarm children), whereas control samples were more "similar" to each other (beta diversity) than asthmatic ones.

The first "direct" link of early-life nasopharyngeal microbiota dynamics and asthma development was reported in 2015. TEO *et al.* [102] investigated the nasopharyngeal microbiome during the first year of life in a cohort of infants. The patterns of microbiota profiles arising during this period were in agreement with other studies [149, 151]. Interestingly, healthy nasopharyngeal colonisation with *Moraxella* and *Streptococcus* spp. in early infancy was associated with early subsequent episodes of more upper and lower respiratory infections, respectively. Importantly, infants who became atopic by the age of 2 years and developed subsequent chronic wheeze at age 5 years were twice as likely to have had early *Streptococcus* spp. colonisation, febrile lower respiratory illness and/or hRV-C wheezing illness in the first year of life, compared with those who did not develop chronic wheeze.

Overall, despite our limited understanding of the respiratory microbiome, its contribution to pulmonary function, respiratory infection and risk of asthma development seems to be

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appreciated. Asthma presence has been correlated with the bacterial microbiota in both the lower and upper respiratory tracts. Early-life colonisation patterns can determine microbiome stability, at least after 2 years of age, even though the respiratory microbiome is possibly still changing during childhood (in contrast to the gut microbiome, which has an adult-like structure from as early as 3 years of age). Events that can interrupt this balance can lead to dysbiosis patterns (affecting the diversity, richness and abundance, rather than the density of microorganisms), which in turn could confine pathogenicity to established bacterial species and/or change the host's immune pressure *ab initio*. Surprisingly, analysis of the viral component of the microbiome, the virome, is still in its infancy, even though the direct and indirect control of prokaryotic and eukaryotic viruses on bacterial populations is evident.

Conclusions

A considerable proportion of chronic lung disease morbidity, mortality and health costs are attributed to exacerbations. Epidemiological studies have convincingly shown that viral respiratory infections are the major cause of exacerbations in both adults and children. Viruses, and hRV in particular, can infect not only the upper but also the lower airway epithelium, resulting in local and systemic immune responses. Deficient innate immune and adaptive responses have been suggested in the pathogenesis of exacerbation, while the emerging role of ILCs is underexplored.

Current therapies are still suboptimal in treating or preventing the infection itself, and subsequently cure or prevent an exacerbation. The relative contribution of viruses and bacteria in asthma/COPD exacerbations, as well as their interactions, remains largely unknown. The emerging role of the nasopharyngeal/lung microbiome and its contribution to pulmonary function, respiratory infection and exacerbation risk may provide novel targets for therapeutic interventions in the context of "united airways diseases".

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Nasal polyposis and asthma: the otorhinolaryngologist's view

Wytske J. Fokkens[1] and Peter W. Hellings[1,2,3]

Asthma patients, especially those with severe asthma, often have CRS with nasal polyps (CRSwNP). In particular, patients with late-onset asthma, high periostin levels and eosinophilia often have CRSwNP. Insufficient control of the upper airways results in insufficient control of asthma and *vice versa*. In severe uncontrolled asthma in particular, the upper airways are often difficult to control. For this reason, it is important that people treating the lower airways, especially for severe asthma, are also experts on the upper airways. CRS has a significant impact on the QoL of the patient, comparable to congestive heart failure and COPD. The pathophysiology of CRS is complex, and includes local, systemic, microbial, environmental, genetic and iatrogenic factors. Severe CRSwNP, mostly with asthma, especially in Europe and the USA, has a type 2 inflammation with IgE, eosinophils and Th2 cytokines, such as IL-5 and IL-4/IL-13. The development of biological therapies has progressed rapidly in recent years and they have been shown to be effective in CRSwNP, as in asthma. Endoscopic sinus surgery has been shown to improve the lower airways and reduce medication use for asthma, and may even prevent asthma from developing.

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Asthma patients, especially those with severe asthma, often have CRS with nasal polyps (CRSwNP). The presence of nasal polyps is associated with the severity of the asthma, regardless of smoking status, ranging from 10–30% in mild asthma to 70–90% in severe asthma [1, 2]. In general, asthma is associated with allergic rhinitis, especially persistent rhinitis, and with CRS in all age groups, in both men and women, and irrespective of smoking behaviour.

Insufficient control of the upper airways leads to insufficient control of asthma and *vice versa*. The upper airways are particularly difficult to control in severe uncontrolled asthma. Thus, it is important that healthcare professionals treating the lower airways, especially for severe asthma, also have expert knowledge on the upper airways. Here, we discuss nasal polyposis

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and asthma from the otorhinolaryngologist's perspective; van der Meer and ten Brinke [3] give the chest physician's perspective elsewhere in this *ERS Monograph*.

What are "CRS", "CRSsNP" and "CRSwNP"?

Rhinitis and sinusitis usually coexist in most individuals; thus, the correct terminology is now accepted to be rhinosinusitis. Most guidelines and expert panel documents have now adopted the term rhinosinusitis instead of sinusitis [4, 5].

The diagnosis of rhinosinusitis is made by a wide variety of practitioners, including allergologists, otorhinolaryngologists, pulmonologists, primary care physicians, paediatricians and others. Therefore, an accurate, efficient and accessible definition of rhinosinusitis is required.

Rhinosinusitis in adults is defined as an inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), combined with facial pain/pressure and/or a reduction or loss of smell, and either endoscopic signs of disease (nasal polyps, disease in the middle meatus) and/or CT changes (mucosal changes within the ostiomeatal complex and/or sinuses) [4]. We refer to CRS when the disease lasts $\geqslant$12 weeks without complete resolution of symptoms, although the symptoms may vary over time. Like asthma, CRS is often a disease with remissions and exacerbations.

Patients who do not reach an acceptable level of control despite adequate surgery, intranasal corticosteroid treatment and up to two short courses of antibiotics or systemic corticosteroids in the previous year can be considered to have difficult-to-treat rhinosinusitis [4]. Although the majority of CRS patients can obtain control, some patients will not do so even with the maximal medical therapy and surgery [6]. In a recent study, adult CRS patients (n=560) in a tertiary centre who had undergone bilateral functional endoscopic sinus surgery (ESS) for CRS 3–5 years prior to the study were evaluated [6]. Only 19.5% of the CRS patients were well controlled, with 36.8% of patients being partly controlled and 43.7% uncontrolled. The levels of control corresponded to mean total visual analogue scale, Sino-Nasal Outcome Test (SNOT)-22 and Short Form Survey-36 scores. Subgroup analysis revealed that female sex, aspirin intolerance and revision functional ESS were associated with a higher prevalence of uncontrolled CRS, whereas allergy, asthma and smoking status did not alter the percentage of patients in each category of control [6].

CRS can be categorised into two phenotypes: CRS without (CRSsNP) and with (CRSwNP) nasal polyps. In CRSwNP, the nasal polyps are bilateral benign masses filled with inflammatory material, which originate from the anterior ethmoid sinus and descend into the nasal cavity. Although it is sometimes possible to see nasal polyps by anterior rhinoscopy, an endoscope is usually necessary for the diagnosis. A CT scan is not helpful in differentiating between CRSsNP and CRSwNP, and in general is only needed when surgery is planned or the diagnosis is unclear. The clinical symptoms of CRSsNP and CRSwNP overlap. However, patients with CRSsNP usually have more problems with facial pain compared with patients with CRSwNP, whereas patients with CRSwNP show more nasal discharge and a decreased sense of smell [7].

In this chapter, we will describe only the relationship between CRSwNP and the lower airways.

Epidemiology of CRSwNP

Recent epidemiological CRS studies have shown a worldwide incidence of between 5% and 12% [8–12]. For CRSwNP, the exact prevalence is more difficult to estimate because of the need for endoscopic evaluation. Using a postal questionnaire in Finland, a prevalence of 4.3% CRSwNP was reported [13]. Using endoscopy, a prevalence of between 2.7% and 5.5% has been reported [14, 15]. When removing the whole naso-ethmoidal block in cadavers, nasal polyps were found in five out of 19 cadavers [16]. Nasal polyps are more frequently seen in men than in women [14, 15], and in elderly and asthmatic subjects [14], and are uncommon in those <20 years of age.

Diseases with a phenotype of nasal polyps and lower airway disease

NSAID-exacerbated respiratory disease, formerly known as aspirin intolerance or Samter's Triad, is a syndrome of airway inflammation characterised by rhinosinusitis with polyposis, asthma and NSAID intolerance. Approximately 9% of patients with asthma will also have AERD, making prompt identification, diagnosis and management of this syndrome important in controlling disease progression [17, 18].

Cystic fibrosis

In CF, bilateral nasal polyps in children are often thought to be a clinical sign of the disease. The prevalence of rhinosinusitis in adult patients with CF is reported to be 63% and the prevalence of nasal polyps 25% [19, 20]. Patients with class I–III mutations had significantly smaller frontal sinuses and sphenoid sinuses, more opacification in the sino-nasal area and more often osteitis/neo-osteogenesis of the maxillary sinus wall, and thus more severe sino-nasal disease, than patients with class IV and V mutations [19]. Rhinosinusitis may often be a presenting symptom of the so-called atypical CF patient with a normal or borderline sweat-test result and carrying only one mild mutation of the CFTR gene [21]. CRS reacts very favourably in new treatments with the novel therapeutic agent ivacaftor, which acts at the CFTR channel to alter activity [22]. Combined sinus surgery and post-operative systemic and topical antibiotic treatment can eradicate pathogenic bacteria from the sinuses of patients with CF and CRS, and significantly improves the lung infection status for at least 3 years; it may also postpone chronic lung infection with Gram-negative bacteria and thus stabilise lung function [23, 24].

CRSwNP can also be found in patients with other diagnoses such as Churg–Strauss disease, polycystic kidney disease and eosinophilic fungal disease.

Association of CRSwNP and asthma

CRS is associated with allergic rhinitis (OR 3.1), especially persistent rhinitis (OR 6.0), and with asthma (OR 3.5), in all age groups, in both men and women, and irrespective of smoking behaviour [25, 26].

The prevalence of CRSwNP in asthma is high, especially in patients with severe asthma. The presence of nasal polyps is associated with the severity of the asthma, regardless of smoking status, ranging from 10–30% in mild asthma to 70–90% in severe asthma [1, 2]. In particular, patients with late-onset asthma, high periostin levels and eosinophilia often have CRSwNP

[27]. The majority of patients with severe adult-onset asthma are nonatopic, have persistent eosinophilic airway inflammation, and have more nasal symptoms and CRSwNP [28].

Impact on QoL and burden to society

CRS generally has a significant impact on the QoL of the patient [29, 30]. Studies have shown that patients with CRS seen in a tertiary care setting suffer a significantly impaired QoL comparable to congestive heart failure and COPD [31]. Although the definition of CRS is based on the symptoms of rhinorrhoea, nasal obstruction, facial pain and a reduction in smell, a wide range of symptoms that extend beyond just sino-nasal symptoms significantly hampers the QoL of CRS patients. The measurement of QoL is thus an important outcome measurement in research [32, 33]. Although the significance of sinus-specific symptoms and QoL is undeniable, there is recent evidence that "extra-rhinological" symptoms, such as poor sleep, fatigue, cognitive dysfunction and overall poor productivity, are as important in the daily life of patients [29]. In contrast to most other otorhinolaryngological disease, no clear differences in socioeconomic variables including social class, index of multiple deprivation and educational attainment are found between CRS patients and controls [34].

While CRSwNP is the less common form of CRS in the population, the majority of CRS patients in tertiary care centres are CRSwNP patients, and most of these patients have asthma. The repetitive need for surgery in CRSwNP patients put a further burden on the healthcare system [33].

While total CRS management costs are estimated to be USD60–65 billion annually [35], there are no studies, to the best of our knowledge, that have provided estimates of direct costs associated with CRSwNP management only.

Pathophysiology of CRSwNP

The upper and lower airways are linked from an anatomical, histological and immunological point of view, with inflammation in one part of the airways influencing the other part and forming a "united airways" system [36]. The new systemic treatment options becoming available make an understanding of the relationship between the upper and lower airways even more important. The main differences in mucosal components are the absence of smooth muscles in the upper airways compared with the lower airways, and the lack of extensive subepithelial capillaries, arterial systems and venous cavernous sinusoids in the lower airways compared with the upper airways.

The pathophysiology of CRS is complex, and includes local, systemic, microbial, environmental, genetic and iatrogenic factors. Heredity is an important factor in the development of nasal polyps. The prevalence in family members of patients with CRSwNP has been found to be 19.2% [37].

In recent years, the role of innate immunity has been emphasised. The first part of the innate immunity that is encountered is anatomical barriers such as mucus and mucociliary clearance and the epithelium. The immune barrier hypothesis proposes that mechanical and innate immune barrier defects are present in CRSwNP and CRSsNP, resulting in increased exposure to foreign material, an abnormal microbiome, and excessive compensatory innate

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cellular and adaptive immune responses. The physical barrier consists of airway mucus that traps foreign matter and intercellular tight junctions between respiratory epithelial cells, forming a semipermeable barrier limiting access across the mucosa. Studies have found that dehydrated mucus, as occurs in patients with CF [38, 39], and increased mucus production [40] can lead to mucociliary clearance dysfunction.

Sino-nasal epithelial cells are able to generate and secrete antimicrobial compounds such as lysozyme, lactoferrin, defensins and cathelicidins, as well as reactive oxygen and nitrogen species (*e.g.* nitric oxide) to directly counteract pathogens [41], and these can be upregulated during active infection [42]. Taste receptors have also emerged as an interesting new explanation of the regulation of innate immune defences. Several cell types in the airway, including ciliated epithelial cells, display chemoresponsive properties that utilise taste receptors. A variety of bitter products secreted by microbes are detected, with resultant downstream inflammation, increased mucous clearance, antimicrobial peptide secretion and direct bacterial killing. Genetic variation of bitter taste receptors also appears to play a role in the susceptibility to infection in respiratory disease states, including CRS [43].

Subsequent studies have suggested a weakened mechanical barrier as well, with diminished tight junction proteins and increased susceptibility to exogenous protease degradation, resulting in a porous barrier in CRSwNP, permitting increased access of foreign material across the epithelium [44–46]. Overall, these data suggest that mucociliary dysfunction is present in both forms of CRS, but a porous barrier is more closely linked to CRSwNP.

An exciting recent development was the discovery of a group of innate immune cells known as ILCs as potential key players in the pathogenesis of CRSwNP and asthma [47, 48]. ILCs do not express antigen receptors, but react promptly to “danger signals” and produce an array of cytokines that direct the ensuing immune response. ILCs are a family of effector cells that are important for protection against infiltrating pathogens and restoration of tissue integrity. Three major subsets have been defined on the basis of their phenotype and functional similarities to Th cells. Group 2 ILCs (ILC2 cells) are known to produce type 2 cytokines, especially IL-5 and IL-13, and are activated by cytokines from epithelial cells such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), which are also associated with type 2 inflammatory responses. Levels of ILC2 cells are highly elevated in nasal polyp tissues in contrast to levels of ILC1 and ILC3 cells, which are diminished [47–49].

Epithelial cells of eosinophilic patients with CRSwNP were shown to have a positive-feedback loop between TSLP, IL-33 and their receptors, enforcing this effect [50]. The Toll-like receptor 3 agonist and viral analogue polyinosinic–polycytidylic acid induces TSLP production in epithelium isolated from nasal polyposis patients, which introduces a mechanism by which the Th2-skewed tissue environment might arise in nasal polyps and invites further evaluation of the potential contribution of current or past viral infections to polyposis pathogenesis [51]. A direct link between IL-25, IL-33 and Th2 cells has been shown, suggesting that IL-172RB1ST21 Th2 cells are likely to contribute to CRSwNP pathogenesis through the IL-25/IL-33 axis [52]. Studies on the role played by IL-25 in the pathogenesis of CRSwNP are accumulating and suggest the possibility of a novel therapeutic strategy for treating CRSwNP [53].

ILC2 cells secrete type 2 cytokines, which protect against parasites and also contribute to a number of inflammatory airway diseases. Depending on the internal environment, ILCs are able to show plasticity to either an ILC1 or an ILC3 type. IL-1β was shown to directly activate human ILC2 cells and IL-12 induced the conversion of these activated ILC2 cells into IFN-γ-producing ILC1 cells, which was reversed by IL-4 [54]. This ILC plasticity was evident in diseased tissues of patients with severe COPD or CRSwNP, which displayed an IL-12 or an IL-4 signature and the accumulation of ILC1 or ILC2 cells, respectively. Eosinophils were a major cellular source of IL-4, revealing cross-talk between IL-5-producing ILC2 cells and IL-4-producing eosinophils [54]. Although the precise roles of ILCs in CRS are still under investigation, it is clear that inhibition of ILC function represents a potential target that could provide novel treatments for CRS.

Recognition of the heterogeneity of CRS has suggested the concept that CRS consists of multiple “endotypes”, defined by distinct pathophysiological mechanisms, which could be identified by corresponding biomarkers.

Originally, CRSwNP was seen as a pure eosinophilic disease, and most research focused on eosinophil-related inflammation [55–57]. The importance of eosinophils was strengthened further by the introduction of the “fungal hypothesis” as the sole cause of CRS. In this hypothesis, toxic mediators secreted by eosinophils play an essential role in the elimination of fungal infection and, as an unwanted side-effect, cause local tissue destruction and CRS-related symptoms [58]. However, it subsequently became clear that CRSwNP can occur in neutrophilic disease.

Polyps found in patients with CF [59, 60] and members of the Asian population [61] display hardly any eosinophilia, and in contrast are relatively neutrophilic. Macroscopically, the polyps of both CF patients and Asian people are indistinguishable from eosinophilic “western” polyps, showing that eosinophilia is not required for polyp formation.

The discovery of neutrophils in CRS has in some ways mirrored their discovery in asthma. Where asthma was once considered a purely eosinophilic disease, it is now clear that neutrophils are prevalent in difficult-to-treat, nonallergic asthma [62, 63].

An interesting study in patients with CRSwNP from Thailand at two time points 12 years apart showed a significant increase in the absolute values of eosinophils and IgE^+ cells in the 2011 CRSwNP tissue series compared with that from 1999, and a significant but smaller increase in neutrophils [64]. This “eosinophilic shift” of inflammation was accompanied by higher *Staphylococcus aureus* carriage, as well as higher frequencies of *S. aureus* invasion (54.8% *versus* 10.6%; $p<0.001$) in the subjects from 2011 compared with those from 1999. Patients with asthma were more likely to have higher *S. aureus* carriage rates compared with nonasthmatic patients [64]. The reasons for this shift are unknown, but it was suggested that the change in lifestyle or diet could contribute. However, recently it was also shown that these differences could be at least partly explained by a genetic component [65].

At present, the aetiology of nasal polyps remains obscure. Nasal polyps represent a chronic inflammatory disease affecting the mucosa of ethmoidal sinus cavities in susceptible individuals, and it can be speculated whether airborne microorganisms would be able to induce or aggravate the inflammation seen in nasal polyps. Although in most patients with CRSwNP the inflammation is characterised by type 2 cells, allergy does not seem to play an important role. The exact cause of the Th2 inflammation has been a source of much speculation in which viruses, *S. aureus* and fungi have been mentioned as potential factors. In recent decades, a number of studies have investigated the potential role of *S. aureus* and the presence of specific IgE directed against *S. aureus* enterotoxins in nasal polyp tissue [66].

Due to their superantigenic activity, enterotoxins may activate inflammatory cells in an antigen-nonspecific way. The rates of colonisation and IgE presence in nasal polyp tissue were increased in subjects with nasal polyps and comorbid asthma or aspirin sensitivity [67]. This topic is also discussed in more detail in the context of the mechanistic paradigm of nasal polyposis and asthma by Bachert *et al.* [68] elsewhere in this *ERS Monograph*.

As well as bacterial enterotoxins, there has been the suggestion of a role of fungi, especially *Alternaria* spp., in the generation of nasal polyps. Due to their capacity to induce eosinophil degranulation, *Alternaria* spp. may contribute to the inflammatory spectrum of CRSwNP/CRSsNP [69]. However, the total lack of effect of antifungal treatment on CRS makes this role less likely [70]. So far, we do not know whether microbial stimuli may represent the aetiology of nasal polyp formation or whether colonisation with microorganisms is favoured in the presence of nasal polyps.

Endotyping of CRS

In recent years, cluster analysis of CRS has shown that, like asthma, CRS is a complex disease consisting of several disease variants with different underlying pathophysiologies [71–73]. Recognition of the heterogeneity of CRS has promoted the concept that CRS consists of multiple groups of biological subtypes, or "endotypes", which are defined by distinct pathophysiological mechanisms that might be identified by corresponding biomarkers. The first attempts to endotype CRS have been structured around Th cells and their downstream events, such as tissue eosinophilia and neutrophilia; this approach involves the cytokines and chemokines related to specific Th cell populations, and related markers such as IgE [71, 72].

In a European cohort, clustering of 173 cases resulted in 10 clusters, comprising four with low or undetectable IL-5, eosinophilic cationic protein, IgE and albumin concentrations, and six with high concentrations of these markers [71]. In the group of IL-5-negative clusters, three clusters clinically resembled a predominant CRSsNP phenotype without increased asthma prevalence, while one cluster had a Th17 profile and comprised mixed CRSsNP/CRSwNP. The IL-5-positive clusters were divided into a group with moderate IL-5 concentrations, a mixed CRSsNP/CRSwNP and increased asthma phenotype, and a group with high IL-5 levels, which mostly comprised a nasal polyp phenotype with strongly increased asthma prevalence. In a second analysis among centres in different parts of the world, there was considerable variability among regions [72]. CRSwNP tissues from patients from Europe, Australia and Japan were Th2 biased, whereas those from Beijing, China, mainly demonstrated mixed Th2/Th1/Th17 patterns, while patients from Chengdu, China, showed even lower Th2 expression. More than 50% of the CRSwNP patients in Europe, Australia and Japan showed a predominantly eosinophilic endotype compared with <30% of patients in Beijing and Chengdu. *S. aureus* enterotoxin-specific IgE was found in significantly greater numbers in patients with CRSwNP from Europe, Australia and Japan, with significantly lower numbers in the patients from China.

An unbiased network-mapping approach using a commercially available immunoassay kit and unsupervised network modelling found associated cytokine–chemokine ("analyte") clusters and "subject" groups, revealing three distinct tissue cytokine–chemokine signatures that could be used to endotype CRS patients and controls [74]. Subject group 1 had no patients with CRSwNP, had fewer asthmatic subjects and was associated most strongly with analyte cluster 3 (chemokines and growth factors). Subject group 2 had the most asthmatic subjects (86%) and all patients (100%) had CRSwNP, and it was associated with analyte cluster 2 (Th2). Subject group 3 was associated with both analyte cluster 1 (Th1/Th17) and analyte cluster 3 (chemokines and growth factors), and had the highest proportion of CRSsNP patients (62.5%). Tissue levels of major basic protein, eosinophilia and CT scores were significantly higher in subject group 2 compared with the other groups.

Interactions between the upper and lower airways

Characterisation of the phenotypes of rhinitis and asthma is very similar, with an emphasis on allergy and eosinophilia, nonallergic phenotypes in both the upper and lower airways, and the link with CRS, especially with nasal polyps and late-onset asthma [75–77].

There are also similarities in endotyping, with an emphasis on type 2 *versus* non-type 2 immune responses. In allergic disease, the prominent endotype is type 2 (Th2 cells, type 2 B-cells, IL-4-producing NKT-cells, basophils, eosinophils, mast cells, ILC2 cells, and IL-4, IL-5, IL-13, IL-25, IL-31 and IL-33) [75, 78]. In general, the type 2 profile is related to a good response to corticosteroids.

Several mechanisms may explain the influence of the diseased nose on the lower airways, *i.e.* altered breathing patterns, pulmonary aspiration of nasal contents, the nasal–bronchial reflex and the uptake of inflammatory mediators in the systemic circulation [79].

The nose acts as a filter and "air conditioner", filtering out particles and warming and humidifying the air, thus protecting the lower airways. A reduction in these functions may lead to increased exposure of the lower airways to allergens. Mouth breathing is independently associated with asthma morbidity [80], indicating that such "air conditioning" can be of major importance. The efficacy of the nose filter depends on the size of the inhaled particles. Small molecules, such as moulds and cat dander, are more associated with an increased risk for asthma, whereas larger molecules, such as tree and grass pollen, are primarily associated with upper airways symptoms. Therefore, the role of preferential mouth breathing in the development of asthma is unclear [81].

Although there is a clear relationship between post-nasal drip and coughing, no direct contact has been proved between nasal secretions and bronchial mucosa. In contrast, after nasal application, deposits of radioactively labelled allergen can be found in the digestive tract but not in the respiratory tract. Stimulation of pharyngolaryngeal receptors is more likely to be responsible for a post-nasal drip-related cough [81]. Interestingly, cough was not induced in rhinitic subjects or healthy controls when artificial post-nasal drip was induced [82].

There is little evidence supporting the naso-bronchial reflex as an important contributor to the unified airways. Nasal allergen challenge can be blocked with a vasoconstrictor but not with lidocaine; moreover, the response of the lower airways after allergen challenge is in general more delayed than would be expected following a naso-bronchial reflex [81].

Allergen provocation studies are a good model to study naso-bronchial cross-talk in allergic airways disease. In patients with allergic rhinitis, segmental bronchial provocation, as well as nasal provocation, induced allergic inflammation in both the nasal and bronchial mucosae [83–85]. Presumably, absorption of inflammatory mediators (*e.g.* IL-5 and eotaxin) from sites of inflammation into the systemic circulation results in the release of eosinophils, basophils and their progenitor cells from the bone marrow [86]. The systemic allergic response is further characterised by increased expression of adhesion molecules, such as vascular cell adhesion molecule-1 and E-selectin, on nasal and bronchial endothelium, which facilitates the migration of inflammatory cells into the tissue [85].

Increases in $CD34^+$ cells capable of eosinophil differentiation, as well as other circulatory mediators (IL-5, eotaxin and cysteinyl leukotrienes), are associated with impaired lung function parameters and enhanced mucosal inflammation in asthmatic patients [86], and these cells react to local corticosteroids in rhinitis patients [87]. Treatment with anti-IL-5 and antibodies to other ILs relevant in the eosinophilic pathway has been shown to be effective in asthma and eosinophilic upper airways disease [88].

Treatment

The various CRS endotypes can be characterised by differences in their responsiveness to different treatments, including topical intranasal corticosteroids and biological agents, such as anti-IL-5 and anti-IgE monoclonal antibodies, and can be based on different biomarkers that are linked to underlying mechanisms [4]. The new possibilities for endotyping are currently of specific interest with the advent of new biologicals, confronting us with the challenge of selecting eligible patients for treatment and predicting their therapeutic response; defining suitable biomarkers is therefore an urgent task.

Precision medicine and control of disease

Considering the complex aetiology of CRS, it is not surprising that effective pharmacotherapy is broad in its spectrum, and most evidence has been accumulated for corticosteroids and antibiotics. Precision medicine is a novel approach, embracing four key features: personalised care based on molecular, immunological and functional endotyping of the disease, with participation of the patient in the decision-making process of the therapy, while also taking into account predictive and preventative aspects of the treatment. Implementation of precision medicine into clinical practice may help to decrease the epidemic of allergies and chronic airways diseases [89, 90].

The goal of CRS treatment is to achieve and maintain clinical control. Control can be defined as a disease state in which the patients do not have symptoms, or where the symptoms are not bothersome, if possible combined with a healthy or almost healthy mucosa and the need for local medication only.

Nasal irrigation

Given that, in CRS, inflammation occurs at the interface of the mucosa with the external environment, suggesting a dysfunctional host–environment interaction [91], it seems logical to target the exogenous agents acting at this interface that drive the secondary inflammatory mechanisms.

Nasal saline is used to clean the nose, getting rid of purulent mucus and crusts that support the vicious circle of new irritation leading to extra inflammation and waste products. The nose itself often is no longer capable of removing this debris from the sinuses because of impaired mucociliary clearance caused by the inflammation and obstruction of the sinus ostia.

Although the evidence is limited, a Cochrane review showed that high-volume isotonic or hypertonic solutions can be beneficial in the treatment of symptoms of CRS, even when used as the sole method of treatment [92]. However, there did not appear to be a benefit from using a low-volume (5 mL) nebulised saline spray over intranasal steroids [92].

Several modifications and additions to the nasal saline irrigation fluid have been investigated. Sodium hypochlorite (NaOCl) is a well-known disinfecting agent effective against several organisms including *S. aureus* and *Pseudomonas aeruginosa*, and a saline solution containing 0.05% NaOCl proved to be significantly more effective than saline alone in CRS patients [93, 94]. Xylitol can reduce nasal bacterial carriage, and rinsing with 12 mg of xylitol dissolved in 240 mL of water resulted in significant improvement of symptoms of CRS compared with saline irrigation [95]. Xylitol 5% reduced biofilm biomass, inhibited biofilm formation and reduced growth of planktonic bacteria (*Staphylococcus epidermidis*, *S. aureus* and *P. aeruginosa*) [96].

The idea that surfactants may dissolve biofilms due to their potential to reduce water surface tension was tested in a nonrandomised open-label trial using nasal irrigations containing baby shampoo and showed 46% subjective symptom improvement [97]. However, a commercialised version of this product was later removed from the market because of possible side-effects in the form of loss of smell.

Nasal rinsing is an important general measure in the treatment of CRS for cleansing the nose and should be seen as a supplement to other more disease-specific therapies [98]. At the same time, additions to nasal irrigation fluid turn it into active pharmacotherapy with promising results, reviving interest in optimal nasal drug delivery techniques [99].

Corticosteroids

Corticosteroids, and especially topical glucocorticoids, are the mainstay of pharmacotherapy in CRSwNP. They directly reduce eosinophil viability and activation, and indirectly decrease the secretion of chemotactic cytokines of nasal and polyp epithelial cells [100]. Biologically, glucocorticoids activate intracellular glucocorticoid receptors, which have α and β isoforms [101]. The α isoform is anti-inflammatory and works by repressing pro-inflammatory and promoting anti-inflammatory gene transcription [102]. The nose has a rich supply of blood vessels. During inflammation, hyperaemia, increased blood flow, microvascular permeability and oedema formation occur quite rapidly.

It has been shown that glucocorticoids exert rapid, delayed and long-term effects on the airway vasculature. The long-term effects are ultimately the consequence of their anti-inflammatory action, and as a result glucocorticoids suppress increased microvascular permeability and oedema formation. However, glucocorticoids also inhibit the expression of vascular endothelial growth factor, and can also considerably decrease blood flow in mucous membrane vessels. This effect appears rapidly, in <5 min, which suggests a nongenomic type of action [102].

Corticosteroid therapy in CRS is used in two modalities: systemic and topical. Systemic therapy makes the drug available throughout the whole paranasal system and is by far the most effective, but carries more risk of side-effects, such as insomnia, weight gain, gastrointestinal disturbance, adrenal suppression, osteoporosis, mood changes and steroid-induced diabetes mellitus [103–105]. Modern topical corticosteroid therapy does not have systemic side-effects, although locally there may be some nasal irritation, dryness of the nose or epistaxis [106, 107]. Adequate delivery and therapeutic effect depend on several factors. For example, delivery is better after ESS as an ostial size of ⩾4 mm is required to begin penetration to the maxillary sinus [108]. Distribution to unoperated sinuses, regardless of the device used, is limited (2–3%), with sprays being the least effective of all [92]. Post-surgery distribution appears to be best with higher volume and positive-pressure devices [92].

A Cochrane meta-analysis on the use of local corticosteroids in CRS (most studies were of CRSwNP) showed improvement for all symptoms, a moderate-sized benefit for nasal blockage and a small benefit for rhinorrhoea [106]. The risk of epistaxis was increased, but these data included all levels of severity; small streaks of blood may not be a major concern for patients. It was unclear whether there was a difference in the risk of local irritation, and there was little information about the effect on QoL [106]. In another Cochrane review, insufficient evidence was found to suggest that one type of intranasal steroid was more effective than another in patients with CRS, or that the effectiveness of a spray differed from that of an aerosol [107]. There was also insufficient evidence to suggest that the different types of corticosteroid molecule or spray *versus* aerosol had different effects [107]. In daily practice, the use of high-volume saline rinsing with local corticosteroid seems to be most effective and has been shown to be safe [109].

Evidence for the use of oral corticosteroids is less extensive, but supports the use of systemic corticosteroids in CRSwNP. Short courses of oral corticosteroids (2–3 weeks) improved health-related QoL and symptom severity in patients with CRSwNP [105]. Oral corticosteroids as an adjunct therapy to antibiotics or intranasal corticosteroids may improve symptom severity, polyp size and condition of the sinuses [104]. It is unclear whether the benefits of oral corticosteroids as an adjunct therapy are sustained beyond the short follow-up period reported (up to 30 days), as no longer-term data were available [104].

With duration of use restricted to several weeks, systemic side-effects are limited. Up to three courses a year are considered good clinical practice and several dosage schemes are used in the literature, with a length of ∼2 weeks, varying from 30–50 mg daily to taper schemes starting at the same dose [104, 105]. Keeping in mind the chronicity of the condition and the potential side-effects of long-term steroid use, one should realise that the effect of systemic corticosteroid use in CRSwNP is temporary. It therefore mainly serves a role in making room for more effective topical intranasal corticosteroid therapy. There is no good evidence showing that surgery is better than repetitive courses of oral corticosteroids [110]. Pre-operative use of local and/or systemic corticosteroids in functional ESS results in significantly reduced blood loss, shorter operative time and improved surgical field quality. Post-operative corticosteroids improve post-operative endoscopic scores in CRS and recurrence rates in cases of CRSwNP [111].

Antibiotics

Interest in using antibiotics in patients suffering from CRSwNP has been sparked by the theory of endotoxin-producing staphylococci as disease modifiers. There are two placebo-controlled trials with short-term, 3-week courses of antibiotics in CRSwNP. A study by VAN ZELE *et al.*

[112] compared methylprednisolone (32 mg daily for 1 week, 16 mg daily for 1 week and 8 mg daily for 1 week) with doxycycline (100 mg daily except the first day of 200 mg) and placebo. Methylprednisolone had a larger but short-lived effect on polyp size and symptoms, while doxycycline had a small but significant and longer lasting effect on polyp size. There was also a significant effect on post-nasal discharge. Statistical analysis between the methylprednisolone and doxycycline groups was not performed. A study by Schalek *et al.* [113] compared oral anti-staphylococcal antibiotics with placebo after ESS. Slightly better but not significant results were obtained for the antibiotic group for symptom-specific and endoscopic scores, as well as for the SNOT-22 QoL measure. Studies of long-term treatment of CRSwNP with antibiotics are generally open studies with often not well-defined study populations, and demonstrate some effect on polyp size and patient symptoms without proper QoL data. There are no data on topical antibiotics in CRSwNP [114].

The role of antibiotic treatment in the medical treatment of CRSwNP seems small and should only be tried when intranasal corticosteroids and saline irrigation have failed to reduce symptoms to an acceptable level. Moreover, one should always bear in mind the potential risk of developing bacterial resistance when applying long-term antibiotics at a low dose, together with physical side-effects and drug interactions.

Treatment with antihistamines and leukotriene antagonist and immunotherapy have not been proven to be effective in reducing signs and symptoms of CRSwNP [4, 115]. Two small studies have shown efficacy of aspirin desensitisation with 300–625 mg aspirin daily in patients with CRSwNP and aspirin intolerance [116, 117]. However daily intake of lower doses did not change the symptomatology or the need for surgery [118].

Biological therapies

As mentioned previously, severe CRSwNP, mostly with asthma, particularly in Europe and the USA, has a type 2 inflammation with IgE, eosinophils and Th2 cytokines, such as IL-5 and IL-4/IL-13. The development of biological therapies has progressed rapidly in recent years, and major advances have been reported for the treatment of allergic diseases and asthma [88].

A number of studies have been performed in CRSwNP involving the antibodies reslizumab (anti-Il-5 [119]), mepolizumab (anti-Il-5 [120]), omalizumab (anti-IgE [121]) and dupilumab (anti-IL-4 receptor α, interfering with both IL-4 and IL-13 pathways [122]). All these studies have shown a positive effect on polyp size, and also on CT score [120–122], symptoms [121, 122], SNOT-22 QoL score [121, 122] and smell testing [122]. The drugs are well tolerated, with limited side-effects. Asthmatic patients in most of these studies additionally achieved significantly improved pulmonary function and asthma symptom reduction.

Biomarkers may allow us to treat patients based on endotyping in a personalised way with far fewer side-effects in severe patients than the present options [89, 90].

Surgical treatment

The association between rhinosinusitis and asthma was discussed earlier. Rhinitis has been shown to be a risk factor for developing asthma independent of atopy. Recently, it has been shown that rhinosinusitis is also a risk factor for developing asthma in the next 5 years

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[76]. As well as improving upper airway symptomatology, the possibility for topical drug delivery [123] and QoL [124, 125], ESS has also been shown to improve the lower airways and reduce medication use for asthma [126–128]. The question of when to operate has recently been addressed by a group of experts. For adult patients with uncomplicated CRSwNP, they suggested that the minimum situation in which surgery can be appropriately offered is when the CT Lund–Mackay score is ⩾1 and there has been a minimum trial of a topical intranasal corticosteroid plus a short-course of systemic corticosteroid with a post-treatment total SNOT-22 score of ⩾20 [129]. Important reasons to carry out surgery, apart from reducing symptoms and improving QoL, are the opening of the sinuses for local treatment and prevention of complications. Surgery is helpful in reducing nasal obstruction and the feeling of pressure in CRSwNP. Symptoms that are difficult to improve are sense of smell and post-nasal drip. The olfactory cleft opacification is a predictive factor of olfactory improvement after surgery in CRSwNP (figure 1) [130].

Two recent meta-analyses have been performed examining asthma outcomes after ESS. They both demonstrated improvements in asthma symptoms, but also underlined that the current literature suffers from suboptimal studies [131, 132].

A very recent study showed that patients with CRS often present with uncontrolled asthma, and ESS improved both Mini Asthma QoL Questionnaire and Asthma Control Test scores. Approximately half of patients with uncontrolled asthma improved after ESS [133]. However, it is unclear whether there are pre-operative factors that can aid clinicians in identifying the patients most likely to experience improvements in asthma QoL or asthma control after ESS.

Recent studies in the UK have shown that patients who receive late sinus surgery for rhinosinusitis reported less improvement in SNOT-22 QoL scores than patients treated at earlier time points, and had greater post-operative healthcare needs and a significantly higher prevalence of asthma (37% asthmatic subjects in patients who were operated on for the first time 5 years after the start of the disease compared with 20% in the group that was operated on in the first year after diagnosis) [134, 135].

A subanalysis of patients with and without asthma indicated that patients in the late cohort without asthma had healthcare needs equivalent to patients in the early cohort with asthma.

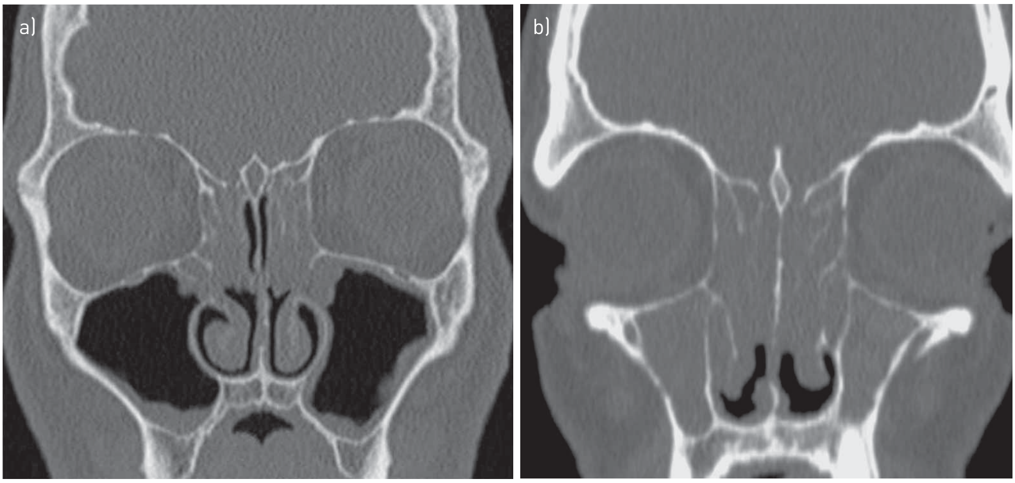

Figure 1. a) Open and b) closed olfactory cleft.

In CF and PCD, it has been shown that sinus surgery postpones chronic Gram-negative lung infection [24]. Surgery is probably also needed to clear the sinus of these bacteria because intravenous antibiotic treatment has substantially lower effects on sino-nasal than on pulmonary inflammatory markers and is insufficient to clear the sinus of these bacteria [136].

Conclusions

The main goal of surgery in patients with CRSwNP is to open the sinus (ethmoid sinus, maxillary sinus and, if needed, frontal sinus and sphenoid sinus) for local treatment. Surgery alone is not enough, and anti-inflammatory treatment with nasal corticosteroids remains necessary. Meta-analyses show improvement of asthma symptoms after sinus surgery.

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Chapter 7

Nasal polyposis and asthma: the chest physician's view

Akke-Nynke van der Meer and Anneke ten Brinke

There is increasing epidemiological evidence linking asthma and CRS, with an even stronger relationship for specific phenotypes, *i.e.* eosinophilic asthma and CRS with nasal polyps (CRSwNP). Asthma patients with concomitant nasal polyposis have more severe disease with reduced asthma control, increased airway obstruction and more extensive eosinophilic inflammation. Different pathways are presumed to lead to this eosinophilic airway inflammation in asthma, whether or not IgE-dependent. Staphylococcal enterotoxin might be the link in the underlying pathophysiology of severe adult-onset nonatopic eosinophilic asthma and nasal polyposis. Patients with uncontrolled, in particular eosinophilic, asthma should be screened for possible CRSwNP in collaboration with an ENT specialist, since various treatment options for nasal polyposis have the potential to improve asthma control. Here, we review the relationship between asthma and nasal polyposis from a chest physician's perspective. Data on epidemiology, pathophysiology, impact on asthma control and clinical assessment are discussed. Finally, treatment options and their effect on asthma outcomes are described.

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Asthma and CRS belong to the most prevalent chronic medical conditions worldwide, with a significant impact on patients' QoL and healthcare costs [1, 2]. Since the concept of the "united airways" was introduced mounting evidence has supported a link between asthma and CRS [3]. Epidemiological studies have shown that asthma and CRS frequently coexist [4], and histopathological data demonstrate similar inflammatory and remodelling characteristics [5].

Asthma is a disease with a variety of clinical presentations [6] and, within this heterogeneous condition, specific subtypes (phenotypes) seem to be associated with CRS [7, 8]. Subgroups within CRS can also be identified and, in particular, CRS with nasal polyps (CRSwNP) is related to asthma [9, 10]. Even though there is increasing support for a relationship between certain subgroups of asthma and CRS, the underlying pathophysiological mechanisms and therapeutic implications are not yet clear. This chapter summarises data on prevalence,

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pathophysiology, impact on asthma control, clinical assessment and treatment options regarding asthma and nasal polyposis from the chest physician's perspective. FOKKENS and HELLINGS [11] discuss nasal polyposis and asthma from the otorhinolaryngologist's perspective elsewhere in this *ERS Monograph*.

Epidemiology

Asthma is a disease characterised by chronic airway inflammation and respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, combined with variable expiratory airflow limitation [6]. It is a serious global health problem affecting an estimated 300 million individuals worldwide, with rising treatment costs, and is becoming an economic burden for patients and the community [12]. Asthma prevalence varies substantially between countries, ranging from 1% to 18% of the population, and is increasing in many developing countries [9, 13]. The development of asthma might be associated with genetic [14] or perinatal factors, atopy [15], obesity [16], and environmental factors including indoor and outdoor allergens [17], viral and bacterial infections [18, 19], cigarette smoke [20], air pollution [21], and occupational exposure [22]. Most of these factors are also implicated as potential triggers for asthma exacerbations, whereby subgroups of asthma patients might be more sensitive to specific triggers (*e.g.* allergens or aspirin). Asthma affects all ages, with a prevalence showing a sex shift during puberty, changing from a higher risk in boys to a higher risk in women after adolescence [9]. Although exposure to environmental irritants might be involved, exposure to allergens is unlikely to account for the higher incidence of asthma in women. Indeed, in a recent large population-based cohort, no sex difference was observed for allergic asthma, whereas the incidence of nonatopic asthma was found to be more than three times higher in women than in men (figure 1) [23]. The high incidence of adult-onset nonatopic asthma in this cohort emphasises the need for more attention to this still poorly recognised subtype of asthma. This might apply especially when considering the relationship between asthma and CRS.

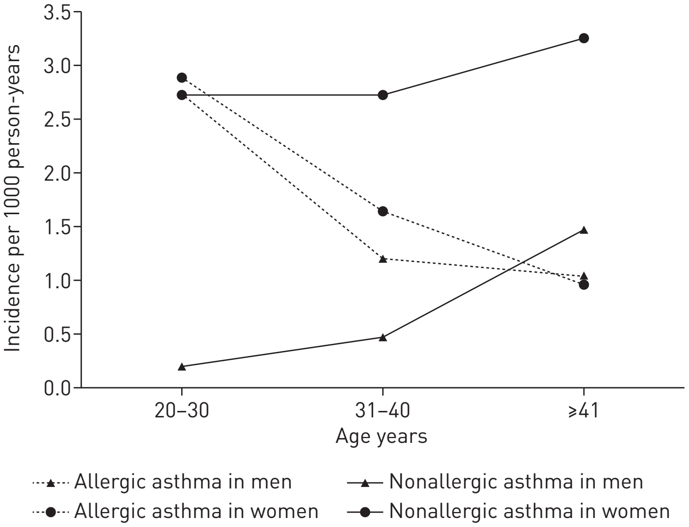

Figure 1. Sex- and age-specific incidence rates for allergic and nonallergic asthma. Reproduced and modified from [23] with permission from the publisher.

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CRS is defined as the presence of at least two symptoms persisting for a period of >12 weeks, wherein radiological or endoscopic documentation of inflammation is required [24]. Symptoms of rhinosinusitis include nasal blockage, purulent nasal discharge, facial pain/pressure and reduction or loss of smell. CRS can be described as infectious or allergic, seasonal or perennial, acute or chronic and with (CRSwNP) or without (CRSsNP) nasal polyps, wherein nasal polyps are described as inflammatory lesions that project into the nasal airway, are typically bilateral and originate from the ethmoid sinus [25]. CRS is present in 5–15% of the adult population [9, 26], and has an impact on QoL comparable to diseases such as COPD and congestive heart failure [27]. The prevalence of CRSwNP is 2–4%, with a higher prevalence in men than women [28]. Nasal polyposis is rare under the age of 20 years and increases with age, with a mean onset between the ages of 40 and 50 years across all ethnic groups. The aetiology of nasal polyposis is still unknown and is considered multifactorial, with several potentially contributing factors such as atopy [29], bacterial or fungal infections [30], or environmental factors, including cigarette smoke and occupational exposure [31]. Nasal polyps are frequently found in aspirin-sensitive patients and an obligatory comorbidity in AERD, a distinct asthma subtype characterised by acute upper and lower respiratory tract reactions to ingestion of aspirin and other cyclooxygenase-1-inhibiting NSAIDs [32, 33].

In addition to asthma and AERD, CRSwNP is often associated with other comorbid respiratory conditions such as CF, PCD and idiopathic bronchiectasis [34]. These associations are the focus of other chapters elsewhere in this *ERS Monograph* [35].

Asthma and CRS(wNP) frequently occur in the same patient. Compared with the general population, CRS is more prevalent in patients with asthma [36] and asthma more frequently diagnosed in patients with CRS [37]. There is a wide variation in the prevalence of asthma observed in patients with CRS, ranging from 20% to 60% [28, 38]. Likewise, the presence of CRS in patients with asthma varies in studies from 40% to 75% [4, 39]. With regard to AERD, the actual prevalence remains uncertain, with numbers ranging from 2% to 25% in asthma and 1% to 22% in CRS, depending on the populations surveyed [40, 41]. These large variations can be attributed to several causes, including changing diagnostic definitions and criteria. Moreover, several of these studies rely on subjective self-reported asthma, AERD or CRS, instead of confirmation by objective measures. Furthermore, asthma and CRS are both heterogeneous diseases with distinct subtypes in which different prevalences may be found.

Initially the asthma–CRS association was mostly described among the allergic population [42], but more recently this was confirmed in the nonatopic subgroup, questioning the role of atopy in this complex relationship [43]. The Global Allergy and Asthma Network of Excellence (GA^{2}LEN) conducted a large multicentre European survey in young, middle-aged and older adults to assess the presence of asthma and CRS defined by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [24]. In all centres, there was a strong association of asthma with CRS (adjusted odds ratio (OR) 3.47, 95% CI 3.20–3.76) independent of age, sex and smoking status [9]. The association with asthma was stronger in those reporting both CRS and allergic rhinitis (adjusted OR 11.85, 95% CI 10.57–13.17). In the nonatopic population, CRS was associated positively with adult-onset asthma (relative risk ratio 3.09, 95% CI 2.51–3.81) and negatively with childhood-onset asthma (relative risk ratio 0.45, 95% CI 0.35–0.57).

Data on the association of asthma with subtypes of CRS are rare and primarily concern CRSwNP. In prospective studies, asthma was found in patients with CRSwNP far more often (26%) than in those without polyps (6%) (OR 5.9, 95% CI 1.79–19.65) [28], independent of atopic status [10]. In a general asthma population, 7–17% of patients also suffer from CRSwNP [44, 45]. The prevalence of CRSwNP is higher in severe asthma, where CT-confirmed CRS could be shown in 24% of patients and was associated with a later onset of asthma [46]. When focusing on the subgroup of patients with severe adult-onset asthma, endoscopically confirmed nasal polyps were present in as many as 54% of the cases, the vast majority of them being nonatopic [47]. In another severe asthma cohort, a similar subphenotype was identified by cluster analysis including patients with later-onset, mostly severe asthma with nasal polyps and eosinophilia [48].

These data suggest that for CRSsNP the association with asthma is most evident in allergic patients, whereas in CRSwNP patients the relationship is strongest with nonatopic adult-onset asthma.

Pathophysiology and triggering factors

Asthma and CRSwNP are both heterogeneous disorders with a complex pathophysiology. They share a number of histological and immunological characteristics, including airway remodelling, Th2 cell induction, IL-5 and IL-13 production, and eosinophilic infiltration [49]. In addition, direct relationships between inflammation in the lower airways and nasal mucosa have been observed [46, 50]. These similarities and associations suggest comparable pathological processes and have contributed to the concept of “united airways disease” [51, 52]. However, despite growing evidence for the link between upper and lower airway diseases, the underlying mechanism is still not clear. This might be partly attributed to the fact that most research up to now has been done in general asthma and/or CRS populations, without taking specific subgroups into account.

The relevance of defining subtypes in asthma has been increasingly recognised, and multiple phenotypes of asthma have been identified based on the inflammatory cell profile, presence of allergy and age at onset of disease [53–55]. In addition to the up-to-now poorly differentiated mixed group of patients without eosinophilic inflammation, distinct asthma phenotypes are distinguished in which eosinophilic airway inflammation plays an important role. In particular, the strongest association with CRS and nasal polyps is found in these eosinophilic subtypes of asthma (figure 2) [47, 56–58]. Eosinophilic inflammation in asthma occurs in allergic as well as nonallergic patients, for which a different underlying pathobiology is presumed. In allergic eosinophilic asthma, allergen-specific induced Th2 cells produce cytokines such as IL-4, IL-5 and IL-13, leading to IgE switching in B-cells and airway eosinophilia [59]. In nonallergic eosinophilic asthma, eosinophilic airway inflammation is considered to be the result of air pollutants, microbes and glycolipids inducing cytokines such as IL-33, IL-25 and thymic stromal lymphopoietin (TSLP), which activate ILC2 cells in an allergen-independent way to produce high amounts of IL-5 and IL-13, leading to eosinophilia (figure 3) [60]. TSLP, an upstream cytokine, may play a central role in eosinophilic inflammation, in allergen-induced as well as allergen-independent asthma [61]. Additionally, TSLP is suggested to be involved in the pathogenesis of nasal polyposis [62] and AERD [63]. Eosinophilia is a characteristic feature of AERD, with increased levels of eosinophils in bronchial mucosa, nasal polyps and peripheral blood [58, 64]. Although the pathophysiology of AERD is not yet fully understood, there appears to be a dysregulation of arachidonic acid metabolism, particularly with an overproduction of leukotrienes, exacerbated by aspirin intake. Together with the increased leukotrienes and reduced prostaglandin levels, an increase

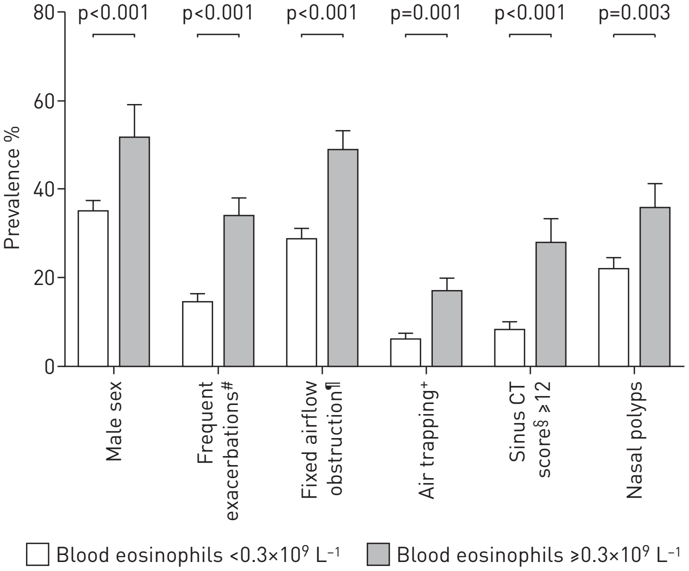

Figure 2. The characteristic profile of adult-onset eosinophilic asthma. Prevalence of distinct characteristics is shown for eosinophilic and noneosinophilic adult-onset asthma patients. #: patients with two or more exacerbations per year; ¶: patients with post-bronchodilator FEV_1/forced vital capacity <70%; +: patients with residual volume/total lung capacity ≥120% pred; §: according to the Lund–Mackay scoring system. Reproduced and modified from [56] with permission from the publisher.

in mast cells and several Th2 cytokines is observed. Thus, different pathways may lead to eosinophilic airway inflammation in asthma, which might also be involved in the pathogenesis of CRSwNP.

In recent years it has been shown that CRSwNP and CRSsNP have different inflammatory patterns in the Western world. CRSwNP is characterised by higher eosinophilia, IgE and IL-5 compared with CRSsNP [65]. Novel evidence indicates that there is considerable heterogeneity also within the CRSwNP subgroup. In Europe, the vast majority of nasal polyps are Th2-driven and eosinophilic, in sharp contrast to the Chinese population in which nasal polyps are mostly neutrophilic showing a Th1 profile [66, 67]. It is still unclear whether genetic or environmental factors drive these differences as different inflammatory profiles can be found even within a single ethnic group [66]. From a chest physician's perspective the subgroup of patients with IL-5-positive nasal polyps is of special interest because the most severe eosinophilic inflammation and comorbid asthma is found in this subgroup [66, 67]. Underlining this, a recent cluster analysis based solely on immune markers assessed in patients with CRS revealed several IL-5-negative clusters without nasal polyps or increased asthma prevalence and distinct IL-5-positive clusters clearly associated with asthma [68]. The group with the highest IL-5 levels consisted of an almost exclusive nasal polyps phenotype with strongly increased asthma prevalence. In this high IL-5 group, two clusters were identified with the highest IgE levels and asthma prevalence, in which all nasal polyps expressed *Staphylococcus aureus* enterotoxin-specific IgE (SE-IgE) [68]. *S. aureus* is a known coloniser of the nasal cavities in Caucasian subjects and is found in the majority of patients with CRSwNP. Eosinophilic inflammation might be intensified by *S. aureus* enterotoxins acting both as antigens stimulating specific IgE responses (SE-IgE) and as superantigens promoting a polyclonal IgE response reflected by an increased total IgE level [29]. Thus, in CRSwNP, but also in asthma, staphylococcal enterotoxin might be

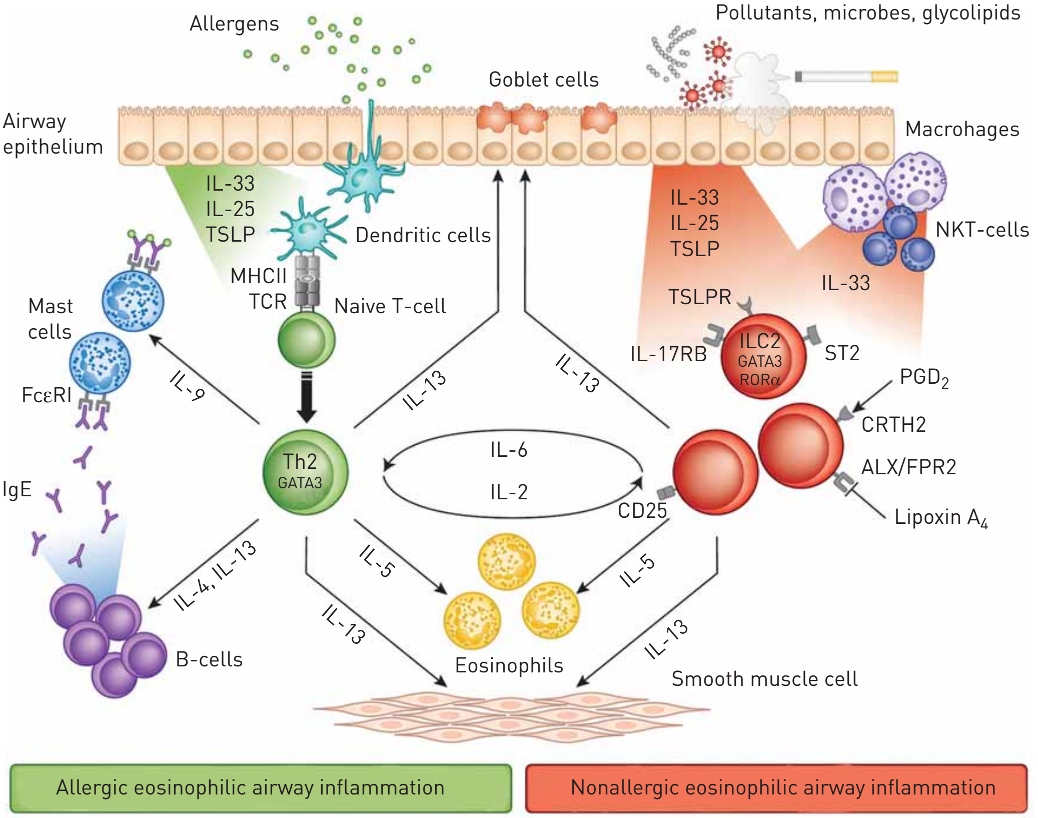
Allergens
Pollutants, microbes, glycolipids
Goblet cells
Airway epithelium
Macrohages
IL-33
IL-25
TSLP
Dendritic cells
IL-33
IL-25
TSLP
NKT-cells
MHCII
TCR
Naive T-cell
IL-33
TSLPR
Mast cells
IL-17RB
ILC2
GATA3
RORα
ST2
PGD2
FcεRI
IL-9
IL-13
IL-13
CRTH2
Th2
GATA3
IL-6
IL-2
ALX/FPR2
IgE
CD25
Lipoxin A4
IL-4, IL-13
IL-5
IL-5
IL-13
IL-13
B-cells
Eosinophils
Smooth muscle cell
Allergic eosinophilic airway inflammation
Nonallergic eosinophilic airway inflammation

Figure 3. Two different pathways lead to eosinophilic airway inflammation in asthma. In allergic asthma, dendritic cells present allergens to CD4$^+$ T-cells, inducing Th2 cells, which produce IL-4, IL-5 and IL-13, leading to IgE switching in B-cells, airway eosinophilia and mucous hypersecretion. In nonallergic eosinophilic asthma, air pollutants, microbes and glycolipids induce the release of epithelium-derived cytokines, including IL-33, IL-25 and thymic stromal lymphopoietin (TSLP), which activate ILC2 cells in an antigen-independent manner *via* their respective receptors (IL-17RB, ST2 and TSLPR). Activated ILC2 cells produce high amounts of IL-5 and IL-13, leading to eosinophilia, mucous hypersecretion and airway hyperreactivity. CRTH2: chemoattractant receptor-homologous molecule expressed on Th2 cells; ALX/FPR2: receptor for lipoxin A_4; FcεRI: high-affinity receptor for IgE; GATA3: GATA-binding protein 3; PGD_2: prostaglandin D_2; RORα: retinoic acid receptor-related orphan receptor-α; MHC: major histocompatibility complex; TCR: T-cell receptor. Reproduced and modified from [60] with permission from the publisher.

involved in the eosinophilic inflammatory process. This concept is confirmed by several studies that have linked high SE-IgE serum levels with an increased risk of not only asthma [69, 70], but also severe asthma [70–72], and have associated its presence with increased levels of total IgE [70]. The level of serum SE-IgE in patients with severe asthma in a Polish cohort was three times higher compared with patients with nonsevere asthma [71]. Aspirin hypersensitivity was highly prevalent in this cohort, particularly in the severe asthma patients, and without exception concomitant with SE-IgE positivity. In another European study the likelihood of having severe asthma was about 11 times higher for SE-IgE-positive *versus* SE-IgE-negative patients. In the subset of nonatopic SE-IgE-positive patients, oral steroid use and hospitalisations were significantly increased and SE-IgE was associated with a lower FEV1 [72]. A recent Korean elderly asthma cohort study showed that high serum levels of SE-IgE were associated with more severe asthma, more sputum eosinophilia and more CRSwNP compared with those with lower SE-IgE levels [73]. Interestingly, SE-IgE was associated with the presence of asthma independent of sensitisation to other allergens.

High levels of SE-IgE were found in 20–30% of patients who tested negative to the regular aeroallergens [71, 72], *i.e.* patients that would be considered nonatopic and up to now formally excluded from treatment with omalizumab. Thus, growing evidence supports the concept that staphylococcal enterotoxin might underlie the pathophysiology of severe asthma, especially the phenotype of adult-onset nonatopic asthma associated with CRS (with or without nasal polyps), high levels of blood and sputum eosinophils, and high serum total IgE [74]. This association is also discussed in more detail by Bachert *et al.* [75] elsewhere in this *ERS Monograph*.

Impact on asthma control

How much impact does the presence and severity of CRSwNP have on asthma severity and control? Several studies have demonstrated a relationship between severity of asthma and the presence of nasal polyps [47, 76]. Amelink *et al.* [47] reported associations between severe adult-onset asthma and nasal polyposis, sputum eosinophil count, exhaled nitric oxide, blood neutrophil count and absence of atopy. van Veen *et al.* [77] also reported difficult-to-treat asthma characterised by persistent sputum eosinophilia, nonatopy and extensive sinus disease. A French group showed that among patients with asthma, those with nasal polyps had reduced asthma control, increased airway obstruction and more extensive eosinophilic inflammation compared with those without nasal polyps [78]. In addition, AERD is also associated with severe asthma. In AERD, asthma is usually preceded by the nasal problems evolving from persistent rhinitis, to refractory CRS, anosmia and recurrent nasal polyps. As the disease worsens, asthma develops and often becomes severe, with reduced lung function, poor asthma control despite extensive treatment and a risk of life-threatening asthma attacks [79].

A subset of patients with asthma is prone to frequent exacerbations, and thus requires special monitoring and treatment. CRS and nasal polyps have both been identified as independent risk factors for frequent exacerbations in several studies around the world, with ORs varying from 1.4 to 5.5 (figure 4) [80–82]. In a recent study identifying clinical features of exacerbation-prone asthma (Severe Asthma Research Program (SARP)-3), chronic sinusitis was again found to be one of the factors associated with exacerbation frequency even after adjustment for multiple factors [82]. Remarkably, African-American patients with CRS more often had nasal polyps than Caucasian patients with CRS, with the increased polyposis being associated with more hospitalisations for asthma [83]. Recently, we reported on risk factors of frequent severe exacerbations in the subgroup of patients with late-onset, eosinophilic asthma, and identified air trapping and high sinus CT scores as independent predictors, suggesting that in these patients inflammations of the distal airways and paranasal sinuses are important predisposing factors for the development of exacerbations [57]. Indeed, there is some evidence that treatment of CRS and nasal polyps might prevent asthma exacerbations. In a management programme including patients with frequent exacerbations, reduction of healthcare utilisation was strongly associated with gastro-oesophageal reflux disease and sinusitis therapy [84]. Outpatient asthma clinic visits were reduced by 50% in the follow-up after sino-nasal surgery [85]. In addition, several studies suggest improved asthma outcomes (including exacerbations) when upper airway inflammation is controlled with medications [39, 86] or treated surgically [87], although the lack of well-controlled studies limits the strength of the conclusions.

Data on the impact of coexisting nasal polyps on lung function in asthma patients are scarce. A French longitudinal study showed that subjects with severe nasal polyps requiring

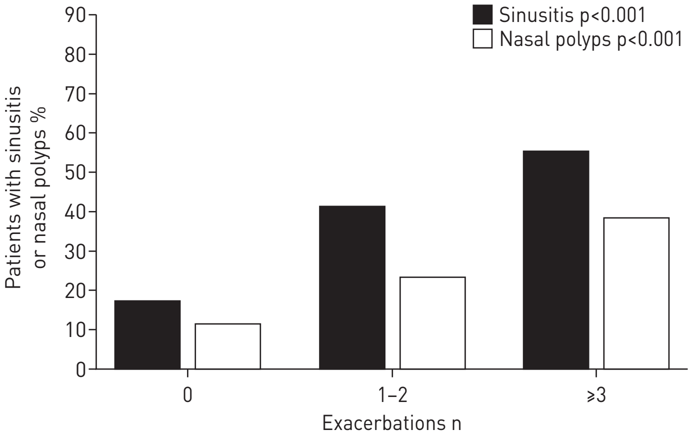

Figure 4. Sinusitis and nasal polyps were significantly associated with exacerbation frequency in a large cohort study identifying clinical features of patients with exacerbation-prone asthma. Reproduced and modified from [82] with permission from the publisher.

nasal surgery exhibited a significant decline in FEV_1 over a 4-year period, unrelated to the presence of nonspecific bronchial hyperresponsiveness or asthma at baseline, or the appearance of asthma symptoms during follow-up [88]. More studies revealed a relationship between the extent of nasal sinus inflammation and lower airway function. In severe asthma, sinus CT scores were positively related to functional residual capacity, a measure of small airway function, particularly in patients with adult-onset asthma [46], suggesting that in this subtype of asthma an inflammatory process involves the whole respiratory tract, from the paranasal sinuses to the very distal airways.

Asthma and CRS have both been linked with an impaired QoL, and comorbid CRS has been identified as a negative predictor of QoL in asthma [89]. Data on asthma and nasal polyps having an accumulative negative impact on QoL are inconsistent, but patients with combined asthma and nasal polyps showed the largest QoL benefit after sinus surgery [90]. Olfactory dysfunctioning is a known symptom in patients with nasal polyps, with a significant impact on QoL. Asthma associated with nasal polyps has an additional impact on the sense of taste and smell, and loss of smell has been proposed as a clinical tool to predict nasal polyposis in patients with asthma [91]. It is noteworthy that some patients with severe asthma, when asked, report significant hearing loss, seriously threatening their QoL. This might be related to a relatively recently recognised middle ear disease, *i.e.* eosinophilic otitis media, characterised by a highly viscous, eosinophil-predominant middle ear effusion causing progressive deterioration of hearing [92]. This otitis is associated with asthma and nasal polyps, is most prevalent in nonatopic subjects, and might be due to mucosal inflammation extending from the lower airways even to the middle ears or be related to local sensitisation to foreign agents (*e.g. S. aureus*) [93]. Hearing loss with recurrent refractory otitis can prompt the physician to consider severe eosinophilic asthma.

Management of asthma patients with nasal polyposis and clinical assessment

In clinical practice, early recognition of concomitant CRS and nasal polyposis in patients with asthma is important, thereby identifying patients at risk of more severe disease, which has clear implications for asthma management. Various items in the history may be of help. If a patient has a history of previous CRSwNP or nasal sinus surgery, recurrence of nasal polyposis might be more likely [94]. In addition, in patients with known aspirin sensitivity or those reporting symptoms of nasal congestion and bronchoconstriction 1–4 h after ingestion of aspirin or NSAIDs, the presence of AERD including nasal polyposis might be considered. However, many AERD patients are unaware of aspirin sensitivity unless provoked [95]. Definitive diagnosis of AERD strictly requires aspirin challenge, although this is not often performed as expensive precautions with respect to safety limit its availability.

The identification of patients with CRSwNP in daily asthma practice may be rather difficult without the help of an ENT specialist and imaging. The characteristic presentation of CRSwNP is gradually worsening nasal congestion/obstruction, fatigue, sinus fullness and pressure, posterior nasal drainage, and hyposmia or anosmia, sometimes with loss of taste. In contrast, fever and severe facial pain are uncommon. Although these symptoms are not specific for CRSwNP, the impaired sense of smell seems a rather predictive symptom in this context and might alert the chest physician to the possibility of nasal polyps [90]. CRS patients may report a variety of other symptoms, such as malaise, cough, sleep disturbance, ear pain or pressure, dizziness, dental pain, dysphonia, or nasal or throat irritation, but all of these lack specificity and are not clinically helpful in diagnosis. Specifically asking for hearing loss and recurrent otitis may prompt the physician to consider eosinophilic otitis media, in particular in adult-onset eosinophilic asthma.

Several questionnaires have been developed to evaluate sino-nasal symptoms, *e.g.* the Sino-Nasal Outcome Test, which are sensitive to changes in symptom severity; however, their usefulness in identifying CRS or nasal polyposis in individual patients in day-to-day practice is limited [96, 97].

Unfortunately, symptoms correlate poorly with objective findings upon imaging or endoscopy, and also physical examination is not of great help to an asthma doctor. Large polyps may be visible with anterior rhinoscopy using a nasal speculum or otoscope (in the hands of a trained clinician), but smaller polyps certainly require nasal endoscopy or imaging. Thus, diagnosis of CRSwNP requires the expertise of an ENT specialist [24].

Clinical evaluation of patients suspected of CRSwNP by an ENT specialist involves routine otolaryngological examination and a detailed endoscopy of the sino-nasal cavity. Inspection of the ears may demonstrate extranasal manifestations, such as eosinophilic otitis media, with important management consequences. Nasal endoscopy can directly visualise the nasal cavities and identify polyps, but also assess the patency of the major ostia and check on purulent drainage from the ostia. Nasal polyps generally begin to form around the ostiomeatal complex, although they may eventually be found throughout the nasal cavities and sinuses, and should be bilateral. Nasal polyps are translucent, yellowish-grey to white, glistening masses filled with gelatinous inflammatory material, the grey-white colour being due to the relatively avascular nature of the polyp tissue.

Noncontrast CT with fine cuts through the paranasal sinuses with bony windowing is the standard protocol for CRSwNP evaluation. A bilateral thickened mucosa is typically observed on sinus CT, in which polyps can be differentiated from nonpolypoid mucosal thickening by their shape and contours. Polyps often protrude as rounded mucosal swellings into the nasal or sinus cavities.

Since CRSwNP is most common in patients with eosinophilic asthma with an adult onset of disease (figure 2) and/or aspirin sensitivity, these patients in particular should be checked for the presence of nasal polyposis. Elevated markers of eosinophilic airway inflammation, including peripheral blood eosinophils and exhaled nitric oxide fraction, may point towards eosinophilic asthma and hint at the possibility of sino-nasal involvement [46]. Therefore, a patient with adult-onset eosinophilic asthma preferably should be referred to an ENT clinic to prove or rule out sino-nasal involvement. In addition, all patients with difficult-to-control asthma should be assessed for the possibility of CRS being the reason for poor asthma control, even in case of absent or only subtle sino-nasal symptoms.

Treatment options

The most recent EPOS revision (EPOS2012) provides a guideline for the treatment of CRS, making a stricter division between CRSwNP and CRSsNP management [24]. This specific treatment guideline applies to CRSwNP patients with or without asthma. It is advised to start the treatment of CRSwNP with intranasal corticosteroids in conjunction with nasal saline irrigation. Intranasal corticosteroids have proven effectiveness on nasal symptoms and nasal polyp size [98]. Patients need to be advised about proper inhalation techniques in order to reduce the risk of local side-effects, *i.e.* nasal irritation and epistaxis. Based on the severity of symptoms, impairment of QoL and extent of mucosal disease, subsequent therapies can be considered on top of topical nasal corticosteroid spray, such as increasing the dose, using nasal drops, or adding antibiotics or oral corticosteroids [24]. Nasal drops might be more effective than sprays due to better distribution within the nasal cavities, in particular after surgery. Regarding antibiotics, a recent Cochrane Systematic Review found very little evidence of their effectiveness in patients with CRS in general, with a slight indication of a modest improvement in QoL in patients with CRSsNP [99]. However, the use of doxycycline is provided as an option in EPOS2012 [24], possibly based on a randomised controlled trial in patients with CRSwNP showing that 100 mg of doxycycline for 3 weeks had a moderate effect on the size of nasal polyps and nasal symptoms [100]. Macrolides have been specifically identified as potentially useful in CRS as well as in asthma due to their anti-inflammatory effects rather than for their antibacterial action [101, 102]. In a heterogeneous CRS group, erythromycin improved all nasal outcome parameters comparable to surgical intervention [103]. Moreover, in a 1-year follow-up of 43 patients with CRS and coexisting asthma, a 12-week course of low-dose erythromycin combined with nasal lavage and fluticasone drops resulted in improvement in asthma symptoms, bronchodilator use, hospitalisations, FEV_1 and levels of exhaled nitric oxide [104]. In the same study, patients randomised to surgery showed similar improvements in asthma outcomes, but erythromycin was found superior to surgery in the subgroup of patients with nasal polyposis. These data suggest that subsets of patients with CRS and/or asthma might benefit from macrolide treatment [102, 105], although possibly not the eosinophilic subgroups, but more research is needed for proper identification. The effect of leukotriene antagonist treatment on clinical outcome measures of CRSwNP was systematically reviewed and showed significant improvements in CRSwNP symptoms over placebo; results that were similar to those found in the nasal corticosteroid treatment arms [106]. There are only two studies in which treatment with the leukotriene receptor antagonist montelukast was studied in CRSwNP with asthma, showing significant improvements in nasal and pulmonary symptoms, asthma medication intake, and sino-nasal inflammation, but no relevant effects on lung function parameters [107, 108]. The beneficial effects appeared independent of aspirin sensitivity, yet leukotriene-modifying agents are administered in most patients with

https://doi.org/10.1183/2312508X.10010116

AERD [109]. In these AERD patients, treatment can be very challenging, with polyposis and asthma often being refractory to medical as well as surgical therapy. Oral aspirin desensitisation followed by daily aspirin administration may improve upper and, to a lesser extent, lower respiratory tract symptoms in selected cases [41]. As in asthma, oral corticosteroids have a beneficial effect on clinical outcomes in patients with nasal polyposis; however, there is some debate on the maintenance of the effect and long-term oral corticosteroid treatment is discouraged in view of the high risk of significant side-effects. Thus, a variety of medical treatments is available, and the challenge is to determine the most beneficial strategy and patient population for the use of the different therapies.

When these medical strategies fail, functional endoscopic sinus surgery (ESS) might be indicated. If so, it is very important that patients are properly informed about the fact that CRS is a chronic condition and have reasonable expectations for treatment [110]. Surgical treatment rarely results in permanent cure and, in particular, in CRSwNP recurrence rates are reported to be as high as 80% [104], with the need for revision surgery being highest in patients with increased eosinophil counts and IL-5 and IgE levels in nasal tissue [111]. Therefore, surgery must be accompanied by medical therapy, since topical steroids slow the recurrence of polypoid inflammation [112]. Together, surgical and medical treatments aim to relieve symptoms and minimise the impact on QoL. In the case of asthma patients it is likewise important to know if improvement in asthma outcomes is to be expected by treatment of CRSwNP. Previously, several authors concluded that available evidence suggested a beneficial effect of both medical and surgical treatment [113, 114], and concerns with respect to possible worse post-operative endoscopic outcomes in asthma patients are no longer shared [115]. Further evidence for the beneficial effects of surgical treatment in patients suffering from both CRS and asthma is given in a recent systematic review [87]. Although reasonable concern regarding quality of the studies was reported, functional ESS for CRS in patients who failed maximal medical therapy appeared to improve clinical asthma outcome measures (figure 5) [87, 116–126]. In general, patients reported improved overall asthma symptoms, decreased use of asthma-specific medications, and fewer hospital admissions and emergency room visits due to asthma exacerbations. Moreover, the cost-effectiveness of functional ESS in severely asthmatic patients with CRS was demonstrated prospectively, with a reduction in outpatient asthma clinic visits of 50% [85]. Thus, both medical and surgical treatments for CRS with concomitant asthma

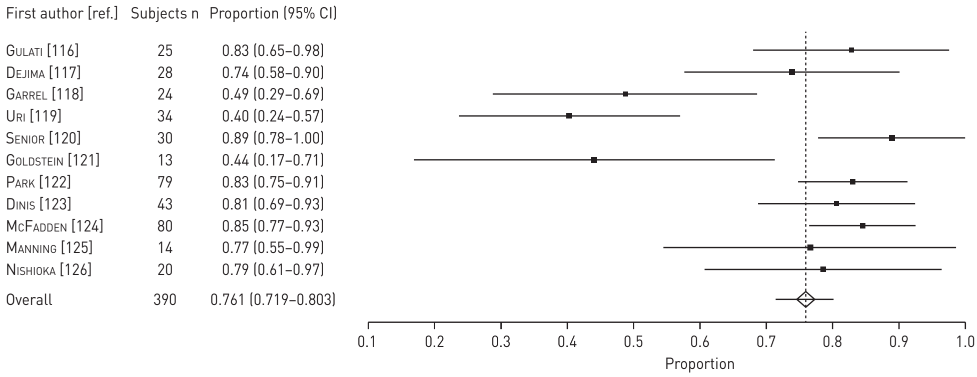

Figure 5. Forest plot of studies examining patient-reported improvement in overall asthma assessment following endoscopic sinus surgery. Reproduced and modified from [87] with permission from the publisher.

improve asthma status, with a possible slight advantage for the medical treatment in cases with nasal polyposis.

Despite all these medical and surgical therapeutic measures, a subset of patients is not adequately controlled, both in terms of asthma as well as in sino-nasal aspects. In particular, patients with severe eosinophilic asthma benefit from novel immunomodulatory therapies, such as anti-IgE, anti-IL-5 and anti-IL-4/IL-13, targeting specific pathological processes. Omalizumab (anti-IgE) proved efficacy in reducing asthma exacerbations and improving QoL in patients with severe allergic asthma, an indication for which it is registered [127]. However, there is some evidence that omalizumab may also have a therapeutic role in nonatopic asthma [128]. In line with this, omalizumab demonstrated clinical efficacy in the treatment of nasal polyps in patients with comorbid asthma, irrespective of the presence of allergy, which the investigators suggested was related to local IgE formation in the upper airways [129]. Several anti-IL-5 therapies have been developed or are currently under investigation for patients with poorly controlled eosinophilic asthma. Many studies have shown that in a select group of asthma patients with severe eosinophilic asthma, inhibition of IL-5 results in clinically important benefits, with significant reductions in steroid dose and a reduced exacerbation rate [130, 131]. There is growing evidence that IL-5 inhibition is, likewise, a potential novel therapeutic approach in patients with severe eosinophilic nasal polyposis. In a randomised controlled trial, 12 out of 20 patients with severe nasal polyposis refractory to corticosteroid therapy who received two single intravenous injections of mepolizumab (anti-IL-5) showed a significant reduction in nasal polyp size and sinus CT score [132]. Remarkably, not all patients with nasal polyps responded to mepolizumab, suggesting IL-5-independent pathways may be involved. This fits in with the clinical observation that some patients with severe eosinophilic asthma and comorbid CRS demonstrate complete recovery of asthma symptoms during mepolizumab treatment, whereas their sino-nasal symptoms persist. Whether anti-IgE treatment would be more successful in these patients remains to be investigated. Several compounds aiming to target IL-4 and IL-13 are now being evaluated and have shown beneficial effects on asthma outcomes [133, 134], as well as also on nasal polyp size in selected patients [135]. Thus, several studies, from the perspective of both asthma and CRSwNP, have shown the promising effects of biologicals in severe airway disease and might be used to avoid daily oral corticosteroid use or repeated sinus surgery in patients.

Conclusions

The goal of this chapter was to explore the relationship between asthma and CRS with nasal polyposis from a chest physician’s perspective. Epidemiological data have already confirmed a link between asthma and CRS, but the recent awareness of subphenotypes of both disease reveals new insights into this association. In particular, for patients with adult-onset nonatopic eosinophilic asthma the presence of CRSwNP seems not to be a comorbidity, but a broadening of the spectrum of the disease. These patients share pathophysiology, severity of disease and poor responses to regular treatment. Several studies have shown promising effects of biological agents in severe eosinophilic upper and lower airway disease. These findings further support the connection between eosinophilic asthma and CRSwNP, and encourage chest physicians and ENT specialists [11] to join forces and work together to find underlying common mechanisms and best treatment options for these severely disabled patients. A major challenge will be to find easily accessible biomarkers to select the patients who have the best chance of a positive therapeutic response to innovative approaches.

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Chapter 8

Nasal polyposis and asthma: a mechanistic paradigm focusing on *Staphylococcus aureus*

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Nasal polyposis and late-onset asthma are mainly characterised by a Th2 immune response, which, although mostly nonallergic, involves increased IgE levels. IgE antibodies found in these patients are predominantly antibodies to *Staphylococcus aureus* enterotoxins, but not inhalant allergens; their expression indicates more severe upper and lower airways disease and airway comorbidity. *S. aureus* is a frequent coloniser of nasal polyps, but has also been shown to reside intramucosally, even intracellularly, and releases secreted proteins which have been demonstrated in the mucosa and correlate with type 2 cytokine production. Apart from enterotoxins, known for their superantigen activity, other secreted proteins such as serine protease-like proteins have been identified as allergens. The secreted proteins are able to bias the immune response to type 2 inflammation, which results in severe impairment of the epithelial barrier and innate immune functions, which consequently eases the survival of *S. aureus*. A better understanding of the role of this microorganism in airways disease is highly warranted.

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The link between the upper and lower airways has long been of interest, derived from epidemiological observations [1, 2], but mainly focused on allergic rhinitis and asthma. Local tissue factors such as the airway epithelium and microbial stimuli and infections, but also systemic inflammatory mechanisms, have been suggested to play a role in the clinical expression of "united airways disease" [3, 4]. Mechanistic observations of this link between the airways boosted the discussion further: when nonasthmatic allergic rhinitis patients were undergoing a segmental bronchial provocation, basophils from the peripheral blood were reduced in numbers, whereas they increased in the bronchi, but also in the nasal mucosa [5].

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In addition, serum IL-5 and blood eosinophils increased in allergic patients after challenge of any compartment of the airways [6], which locally upregulated adhesion molecules to attract those cells from the blood; this indicated that the bloodstream might link the different organs.

Furthermore, the finding that progenitor cells also could use the bloodstream to reach active allergic areas of the airways introduced the bone marrow into the equation [7]. The bone marrow was shown to release $CD34^+$ progenitor cells that finally differentiate into mast cells, basophils and eosinophils at the organ sites of the allergic reaction [8]. Circulating $CD34^+$ cells expressed receptors for thymic stromal lymphopoietin (TSLP) and IL-33, possibly derived from ILC2 cells of the innate immunity, and responded to these cytokines by rapidly releasing high levels of IL-5 and IL-13. Activated $CD34^+$ cells could be detected in the sputum of allergic asthmatic subjects and numbers increased in response to specific allergen inhalation. Thus, distributing over the bloodstream and attracted by the release of local chemokines, these cells are likely to contribute to the manifestation of allergic inflammation in different compartments of the airways. Although not specifically demonstrated for other type 2 inflammatory diseases of the airways such as nasal polyposis and late-onset asthma, the same mechanisms very likely also apply in these cases.

The available epidemiological observations on the so-called “asthma comorbidity” in CRS without nasal polyposis (CRSsNP) or with nasal polyposis (CRSwNP) were recently summarised [9]; however, differentiation between those two major phenotypes of CRS was insufficiently described. Today, asthma comorbidity in CRSwNP patients has been reported to be as low as 7% (*e.g.* in parts of China) to as high as ⩾45% (in Europe, the USA and Australia), in parallel with the expression of a type 2 inflammatory inflammation within the polyp tissue [10]. In Europe, there is a clear association between asthma and (not further defined) CRS, as shown in the Global Allergy and Asthma Network of Excellence (GA^2LEN) study involving 52 000 subjects aged 18–75 years [11]. A postal questionnaire in representative samples of adults living in Europe was used to estimate CRS prevalence as 11.9% of the European population; furthermore, there was a strong association of asthma with CRS at all ages. CRS in the absence of nasal allergies was positively associated with late-onset asthma [11]. Of great interest, we also observed this phenomenon in a recent Europe-wide GA^2LEN sinusitis cohort study (unpublished observation); again, nasal polyposis patients typically suffered from late-onset often nonallergic asthma, with either of them diagnosed first, whereas allergic rhinitis subjects suffered from early-onset allergic asthma. However, early-onset asthma and allergy can also be observed in CRSwNP, but rather as an independent disease, not impacting on the inflammatory profile of the upper airways.

The question therefore arises what else apart from inhalant allergens may drive this comorbidity of CRSwNP with asthma, obviously able to induce even higher amounts of mucosal IgE and an often severe eosinophilic “type 2” inflammation?

The signature of *Staphylococcus aureus* in CRSwNP and asthma

With the support of Gunnar Johansson (Department of Clinical Immunology, Karolinska Hospital, Stockholm, Sweden), who developed a specific immunodiagnostic tool to detect IgE to several *S. aureus* enterotoxins (SE-IgEs), we investigated a small group of clinical CRSwNP samples and found SE-IgEs in about half of the patients [12]. The SE-IgE-positive group had high total IgE concentrations in the tissue, a severe eosinophilic inflammatory reaction and frequent asthma comorbidity. From this first observation in airway disease to the hypothesis of *S. aureus* as an initiator of severe inflammation in CRSwNP [13], a wide range of epidemiological as well as mechanistic studies have been performed by us and others [14], confirming the potential causal role of *S. aureus* and its secreted proteins not only in CRSwNP, but also in asthma. This does not exclude the role of other microorganisms being of importance in this disease.

Colonisation and intramucosal presence of *S. aureus* and its secreted proteins

It was observed as early as 2004 that nasal polyps were frequently colonised by *S. aureus* [15], whereas this was not obvious for the bronchi in asthma; however, in the upper as well as the lower airways, it was noted that macrophages were insufficiently clearing *S. aureus* from the airways [16, 17]. In an unpublished bronchial biopsy study (P. Howarth, University of Southampton, Southampton, UK), we observed macrophages with intracellular *S. aureus* in healthy, but extracellular biofilm-forming bacteria in severe asthma subjects. Of note, it takes only a few *S. aureus* bacteria to induce and maintain an immune reaction, as we will discuss later in this chapter.

S. aureus has been repeatedly found intramucosally, even intracellularly, in macrophages, mast cells and epithelial cells in CRSwNP, but not other tissues [18–20]; we recently also succeeded in demonstrating that secreted proteins from the immune proteome of *S. aureus* can be found in CRSwNP tissues [21]. In total, more than 600 *S. aureus* proteins were identified by high-resolution mass spectrometry or multiple reaction monitoring in nasal polyp tissues directly collected from patients. IgA- and IgG-specific antibody signals were also profiled for 115 *S. aureus* proteins. Strong antibody signals were predominantly found for surface or secreted proteins; among those were also antibodies against superantigens such as SEA, SEB, SEC, SEK and toxic shock syndrome toxin (TSST)-1. It is obvious that the local immune response in this chronic inflammatory reaction does not eliminate intracellular persisting *S. aureus* nor does it abolish *S. aureus* carriage. The antibodies will exert their biological effector functions upon binding to their specific bacterial antigens, which will induce pro-inflammatory processes such as complement activation [22]. Moreover, local T-cell responses may be triggered by superantigens and other antigens, leading to cytokine release of Th1/Th17 cells, but also Th2 cells, depending on the nature of the antigen and the predisposition of the host. In fact, the frequency of carriage is strongly increased in nasal polyp patients, as discussed previously [15]. It is therefore likely that *S. aureus* and the innate and adaptive immune responses directed against it contribute to the chronic recalcitrant inflammation of the airways. This notion is supported by the strong relationship between the presence of IgE immune responses to staphylococcal proteins and the severity of disease in upper and also lower airways diseases. Similarly, for atopic dermatitis, *S. aureus* density on lesional *versus* nonlesional skin appears to be associated with disease severity [23].

S. aureus drives IL-5 production in polyp tissue

In a further step to demonstrate that *S. aureus* residing within nasal polyp tissue in CRSwNP patients does impact inflammation, we analysed CRSwNP tissue freshly obtained during routine surgery, which did or did not contain cultivatable *S. aureus*, and studied spontaneous IL-5 production by nasal polyp tissue over 24 and 72 h in tissue culture. In *S. aureus*-positive samples we interfered by killing the bacteria using antibiotics or *S. aureus*-specific ISP bacteriophages, either active or heat inactivated. Finally, phage-neutralising antibodies were

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used to demonstrate the specificity of the phage-mediated effects. We monitored the number of colony-forming units of *S. aureus* and identified secreted *S. aureus* proteins by mass spectrometry [24].

For the first time we demonstrated that cultivatable *S. aureus* could be found in type 2 inflamed nasal polyps; the pathogen replicates within 24 h and secretes proteins, including superantigens and serine protease-like proteins (discussed in more detail later in this chapter). The presence of *S. aureus* was associated with a significantly higher spontaneous release of IL-5. Killing of *S. aureus* by antibiotics or specific bacteriophages significantly reduced or abolished the IL-5 release. The suppressive activity of the bacteriophage on IL-5 production could be abolished by heat inactivation or anti-phage antibodies, demonstrating the specificity of the effect of the bacteriophage. These experiments undoubtedly indicate a direct role of *S. aureus* in the regulation of IL-5 production in nasal polyps and suggest the involvement of bacterial proteins detected in the tissues [24].

Classical superantigens and IgE formation

The classical superantigens released from intramucosal microorganisms are known to induce a "cytokine storm"; however, as they are released in low quantities, they contribute to chronic inflammation, but do not induce shock, as has been described with nasal or vaginal tamponage. Exposing normal nasal mucosa, but specifically nasal polyp tissue, to classical superantigens elicits strong cytokine production, including Th1, Th17 and Th2 cytokines [25]. Specifically, IL-4 and IL-13 may contribute to the strong polyclonal IgE formation that is observed in nasal polyps; extranodal lymph follicles have been demonstrated in nasal polyp tissues, as well as all necessary ingredients to locally switch to IgE formation such as activation-induced cytidine deaminase, BAFF (B-cell-activating factor of the tumour necrosis factor (TNF) family), and the recombination-activating genes *RAG1* and *RAG2* [26–29]. Of interest, switch circle transcripts revealed ongoing local class switch recombination to IgE, and the expression of RAG1 and RAG2, required for receptor revision, correlated with the magnitude of inflammation and the presence of SE-IgE in the nasal polyp mucosa [29]. Recently, it was elegantly demonstrated that superantigens can indeed activate basophils (and mast cells) by simultaneously binding as antigens in the conventional manner and as superantigens to framework regions of anti-SEE-IgE in anti-SEE-IgE–FcεRI complexes [30]. SEB-IgE as well as allergen-specific IgE present in the polyp tissue is functional and thus contributes to the chronic activation of mast cells (figure 1) [31]. Furthermore, the presence of SE-IgE in tissue or serum may serve as proof of prior contact of the patient with *S. aureus* enterotoxins, and may therefore be used as a marker of interaction with superantigens and possibly severe inflammation. As a diagnostic tool, we and others have therefore used it in airway diseases.

SE-IgE as a diagnostic marker in tissue and serum

With the first description of the SE-IgE immunoassay capture ("ImmunoCAP") test used in tissues of nasal polyp patients [12], a tool was created that allowed studies in tissues and sera in various populations of airway disease patients.

SE-IgE in nasal polyp tissue predicts asthma

Possible biomarkers of asthma comorbidity were analysed in nasal polyp tissues from 70 European and 93 Chinese patients, 34% and 8% with comorbid asthma [32]. A classification

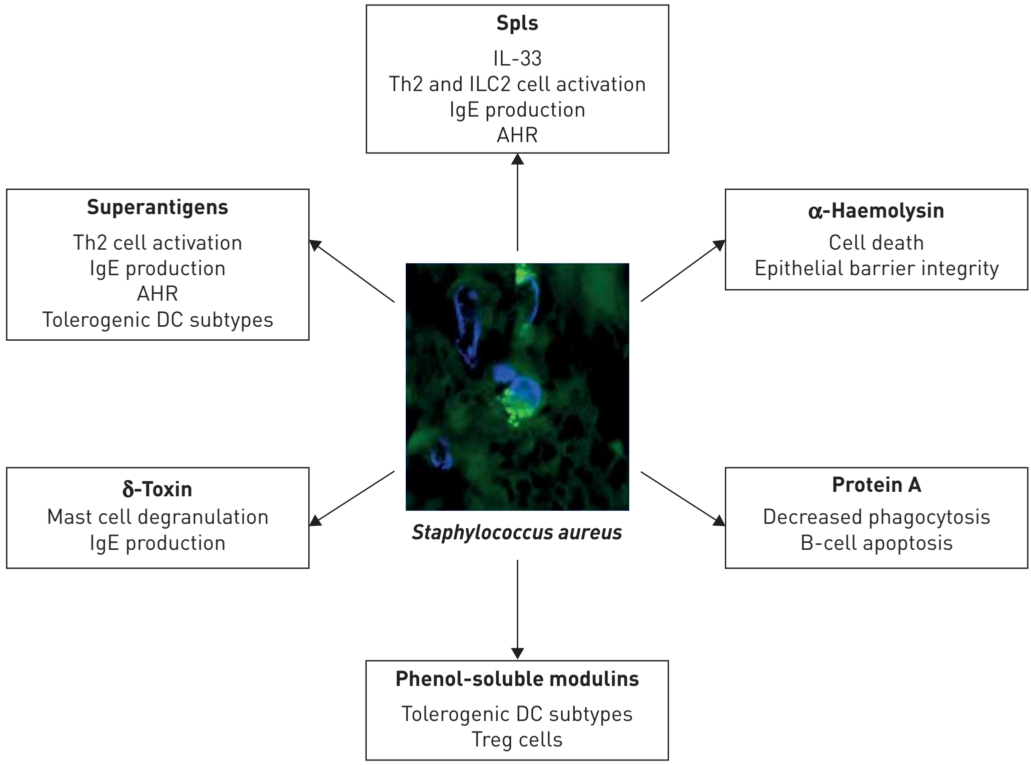
Spls
IL-33
Th2 and ILC2 cell activation
IgE production
AHR
Superantigens
Th2 cell activation
IgE production
AHR
Tolerogenic DC subtypes
α-Haemolysin
Cell death
Epithelial barrier integrity
Staphylococcus aureus
δ-Toxin
Mast cell degranulation
IgE production
Protein A
Decreased phagocytosis
B-cell apoptosis
Phenol-soluble modulins
Tolerogenic DC subtypes
Treg cells

Figure 1. Possible strategies for *Staphylococcus aureus* to affect type 2-biased inflammation. Several secreted components of *S. aureus* may affect type 2 inflammation. The mechanisms include induction of airway hyperreactivity (AHR), stimulation of type 2 cytokine production by airway epithelium, Th2 cells and ILC2 cells, production of IgE and degranulation of mast cells, and induction of tolerogenic dendritic cell (DC) subtypes and Treg cells. Spl: *S. aureus* protease-like protein.

tree evaluation identified IL-5 as the main positive determinant; 83% of the European and 16% of the Chinese polyp tissues expressed the type 2 cytokine. SE-IgE in tissue was associated with significantly increased total IgE and eosinophil cationic protein (ECP) concentrations in both populations. Expression of SE-IgE within the tissue, total tissue IgE $>1440\ \mathrm{kU{\cdot}L^{-1}}$ and ECP $>17\,109\ \mathrm{mg{\cdot}L^{-1}}$ in samples with a total IgE concentration $>246\ \mathrm{kU{\cdot}L^{-1}}$ significantly predicted asthma (odds ratio 5.8–13). Thus, SE-IgE was not only a marker for severe inflammation in nasal polyps, it also predicted asthma comorbidity in CRSwNP subjects and could serve as a link between upper and lower airway diseases. These findings were in agreement with the findings of a study of bronchial and nasal biopsies demonstrating significantly higher concentrations of Th2 cytokines in nasal polyps compared with inferior turbinate and bronchial biopsies [33]. At the same time, the inflammatory profile of nasal polyps and bronchial biopsies correlated significantly ($p<0.01$), indicating that the sinuses may contribute to inflammation in the entire airways.

SE-IgE in asthma cohorts and asthma severity

Adult cohorts of 69 control subjects, 152 patients with nonsevere asthma and 166 patients with severe asthma (defined as inadequately controlled disease despite high-dose inhaled corticosteroids plus at least two other controller therapies, including oral steroids) were analysed for blood biomarkers [34]. Serum SE-IgE positivity was significantly greater in patients with severe asthma (59.6%) than in healthy control subjects (13%; $p<0.001$). Logistic regression analyses demonstrated significantly increased risks for SE-IgE-positive subjects to have any asthma (OR 7.25, 95% CI 2.7–19.1) or severe asthma (OR 11.09, 95% CI 4.1–29.6) *versus* SE-IgE-negative subjects. The presence of grass pollen or house dust mite (HDM) IgE antibodies was not associated with either risk. Oral steroid use and hospitalisations were significantly increased in patients with SE-IgE and in nonatopic asthma subjects. SE-IgE was also associated with a lower lung function measured as FEV_1 % predicted. SE-IgE, but not IgE against inhalant allergens, was thus identified as a risk factor for asthma severity in both the allergic and nonallergic populations. Again, the presence of SE-IgE in serum indicated the involvement of staphylococcal superantigens in the pathophysiology of severe airway disease.

The GA^2LEN survey in Europe described earlier [11] was again used to study a random sample of 2908 subjects by skin prick tests for common aeroallergens and blood total IgE and SE-IgE measurements [35]. Prevalence of positive SE-IgE was 29% and more common in smokers (<15 pack-years OR 1.33, 95% CI 0.97–1.84; $p=0.079$ *versus* ⩾15 pack-years OR 1.87, 95% CI 1.34–2.60; $p<0.001$). SE-IgE was associated with asthma (OR 2.10, 95% CI 1.60–2.76; $p=0.001$) in a concentration-dependent manner. This study demonstrated for the first time that SE-IgE was significantly and independently associated with asthma in the European population.

Similar findings were reported in a study of Korean urban and rural populations consisting of 1080 adults (mean age 60.2 years) [36]. Positive SE-IgE had a prevalence of 27.0% in serum; risk factors were identified as male sex, current smoking, advanced age (⩾61 years) and inhalant allergen sensitisation. Current asthma was mostly adult onset (⩾18 years old) and showed independent associations with high SE-IgE levels in multivariate logistic regression tests. These findings were confirmed in an independent even older population of 249 patients with late-onset asthma and 98 controls aged >65 years [37]. Elderly asthma patients with high SE-IgE levels were characterised by more severe asthma, sputum eosinophilia and CRS compared with those with lower SE-IgE levels. The association between serum SE-IgE concentrations and severe asthma was significant and independent of covariables in multivariate logistic regression analysis (OR 7.47, 95% CI 1.86–30.03; $p=0.005$) in SE-IgE-high ($\geqslant 0.35\ kU \cdot L^{-1}$) *versus* SE-IgE-negative ($<0.10\ kU \cdot L^{-1}$) patients.

Multiple correspondence analyses also showed that high serum SE-IgE level had close relationships with severe asthma, CRS and sputum eosinophilia. The paper by SONG *et al.* [37] prompted an Editorial by CHUNG [38] entitled "Staphylococcal enterotoxin-specific IgE: a biomarker for a distinct phenotype of severe asthma?" that indicated the possible role of SE-IgE as a predictor of response to omalizumab in nonatopic late-onset asthmatic subjects, which needs further study. As mentioned earlier, SE-IgE was identified as a risk factor for asthma severity in both allergic and nonallergic populations [34], and these patients are likely to respond well to omalizumab [39].

S. aureus is an active immune modulator to type 2 inflammation

S. aureus is a versatile bacteria frequently found colonising patients with type 2-biased diseases such as atopic dermatitis and CRSwNP. Compelling evidence exists showing that *S. aureus* enterotoxins act as modifying agents in the inflammatory response in upper and lower airway diseases [40, 41]. *S. aureus* actively manipulates the host immune response by releasing proteins that facilitate bacterial invasion and colonisation, and have immunomodulatory properties (figure 1) [42, 43]. As *S. aureus* has been identified as a major cofactor in atopic disease, it is important to understand the interplay between *S. aureus* and its products with the immune response of the host, and to elucidate its role in the initiation and persistence of chronic airway disease.

S. aureus protease-like proteins induce type 2 immune response

Six Spls (A–F) belong to a small subfamily S1B, encompassing staphylococcal V8 protease, epidermolytic toxins and Spl proteases. They share high sequence similarity and contain putative signal peptides of 35–36 amino acids [44]. 84% of *S. aureus* strains contain at least one Spl protease-encoding gene [45]. Stentzel *et al.* [46] demonstrated that healthy carriers have increased levels of IgG1 and IgG4 antibodies to all Spls in the blood. Importantly, the levels of IgE antibodies to all Spls, except for SplC, were significantly higher in sera of asthmatic patients compared with controls, demonstrating a strong link between the immune response to Spls and atopic status. SplD induces a type 2 immune response with typical features of asthma, such as airway hyperreactivity, goblet cell hyperplasia, Th2 cytokine production and IgE antibody response, in mice [47]. Likewise, SplF, which has 95% sequence homology with SplD, induces strong type 2-biased airway inflammation [47]. Inhalation of allergens with proteolytic capacities such as HDM leads to asthma *via* initiation of the Toll-like receptor 4 (TLR4) signalling pathway [48]. In contrast to HDM-induced allergic asthma, SplD induces airway eosinophilia and specific IgE production in a TLR4-independent manner. The mechanisms of Spl sensing are not entirely clear and need further investigation. The SplD-induced allergic features could be antagonised by soluble IL-1 receptor-related protein ST2 intratracheal treatment, suppressing the IL-33-mediated activation of eosinophils, ILC2 cells, production of type 2 cytokine in the local lymph nodes and reduced airway hyperreactivity, thereby attenuating allergic asthma symptoms in mice [47]. In addition to aggravating allergic airway inflammation, SplD alters epithelial airway integrity, facilitating access of other allergens and pollutants to the innate immune system.

It is important to understand the interplay between the immune proteome of *S. aureus* and the immune response of the host, and to elucidate its role in the initiation and persistence of chronic airway diseases. Apart from acting as an allergen, SplD is capable of inducing specific IgE production to an inert protein, thus acting as an adjuvant responsible for the broadening of the allergic immune response [47]. This observation supports epidemiological studies showing that exposure to some *S. aureus* secretome proteins, including enterotoxins or Spls, concurrent with allergen exposure could be a common factor leading to asthma susceptibility. A similar action was ascribed to *S. aureus* enterotoxins, which were shown to break tolerance to inert proteins and induce a type 2-biased allergic immune response in mice [48, 49].

S. aureus-induced tolerogenic dendritic cells and Treg cells

Accumulating data suggest that *S. aureus* could produce immunomodulatory molecules promoting either immune tolerance (anti-inflammatory response) or pro-inflammatory responses. A pro-Th2 anti-inflammatory response provides a distinct advantage for *S. aureus* survival, thus facilitating bacterial persistence and chronicity of disease. The *S. aureus* secretome was shown to promote Th2 inflammation and inhibit the modulatory function of resident Treg cells *in vitro*, while *Staphylococcus epidermidis* was able to induce competent Treg cell production and induction of Th1 cytokines in the inflammation, therefore counteracting the type 2 immune response [50]. *S. aureus* phenol-soluble modulin (PSM) peptide toxins induce tolerogenic dendritic cells producing IL-10 with impaired capacity to induce activation and proliferation of $CD4^+$ T-cells, while increasing the numbers of Treg cells [51]. SEB also induced dendritic cell maturation and promoted Th2 polarisation *in vitro* [52]. Along with the generation of suppressive antigen-presenting cells, *S. aureus* secreted proteins, such as SEA, possess the ability to convert neonatal conventional T-cells into Treg cells and to support Th2 polarisation [53–55]. Furthermore, *S. aureus*-derived lipoteichoic acid suppresses T-cell cytokine production [56].

It has been estimated that the *S. aureus*-specific T-cell pool may comprise up to 3.6% of T-cells in healthy individuals [57]. *S. aureus*-specific T-cells produce Th1, Th17 and Th2 cytokines upon *S. aureus* antigen re-stimulation, therefore affecting the course of *S. aureus* infection. Several *S. aureus* virulence factors, such as δ-toxin, δ-haemolysin, and PSMα1 and PSMα3, promote type 2 immune responses by inducing a dose-dependent activation of mast cells and exacerbating allergic disease [58–60]. Mast cells in the nasal mucosa of CRSwNP patients were shown to contain intracellular *S. aureus*, therefore protecting the bacteria from antimicrobial actions and establishing an intracellular reservoir that contributed to the chronic carriage in CRSwNP [20]. These findings provide new insights into the role of the mucosal microbiome in the airways, and its interplay with mucosal immune cells, which could modulate the inflammatory response towards type 2-biased inflammation.

Eosinophil extracellular traps in response to *S. aureus*

Eosinophils are abundantly present in Th2-biased upper airway pathologies such as asthma and CRSwNP. They are terminally differentiated granulocytes, playing a role in innate host defence against pathogens through the release of toxic granule proteins and reactive oxygen species. Through the release of their toxic contents, they can damage both pathogenic and host cells. For this reason, eosinophils have long been considered as harmful cells and, unsurprisingly, their presence in tissue or airway secretions is positively associated with the severity of both asthma and CRSwNP [61, 62]. In addition to their well-known cytotoxic activities, it is now clear that eosinophils play a role in both innate and adaptive immunity *via* different effector mechanisms. Furthermore, eosinophils can contribute to antibacterial defence by releasing DNA in association with granule proteins. These so-called eosinophil extracellular traps (EETs) are able to bind and kill bacteria [63]. *In vitro*, eosinophils are triggered to form EETs after stimulation with IL-5, TSLP, eotaxin and C5a [64]. Interestingly, co-culture of eosinophils with *S. aureus* causes a rapid generation of EETs in the absence of any additional stimuli. Under these *in vitro* conditions, EETs are able to entrap *S. aureus* and inhibit its growth *in vitro* [63, 65]. Moreover, the exposure of eosinophils to TSLP, reported as an important regulator in both CRSwNP and asthma pathogenesis, also results in the release of EETs *in vitro*. TSLP-evoked EET generation seems to be dependent on CD18 and CD11b adhesion [65, 66].

The presence of extracellular nucleases as a defence strategy against DNA traps in several pathogenic bacteria, including *S. aureus*, *Clostridium perfringens* and *Streptococcus pyogenes*, provides further evidence for the pathophysiological relevance of EETs in a number of pathogenic conditions. In addition, a streptococcal DNase has previously been implicated in disease progression [67].

The presence of EETs has been shown in multiple eosinophilic diseases, including secretions from eosinophilic asthma and CRSwNP patients [68, 69]. EETs were shown to contribute to the properties of highly viscous eosinophilic mucin and impairment of its clearance in CRS; similar viscous mucin is also typical for asthma [69, 70]. We recently demonstrated the presence of EETs targeting *S. aureus* at the epithelial layer, especially at epithelial barrier defects in CRSwNP; EETs can also be found above the epithelium within nasal secretions [71]. When eosinophils are brushed from the epithelium and exposed to *S. aureus*, they rigorously release EETs (figure 2). In nasal polyps, we showed a positive correlation between EETs and periostin in tissue, involvement of reactive oxygen species in EET generation *in situ*, and active migration of eosinophils towards and entrapment of *S. aureus in situ* within a 2-h time frame [71]. These findings yield new insights into the possible role of EETs, and by extension of eosinophils, in human airways, and link *S. aureus* to eosinophilic airway disease such as CRSwNP and comorbid asthma. Thus, the formation of these EETs could be viewed as a double-edged sword providing an important mechanism of host immunity against infections and simultaneously causing damage to cells and tissue.

Damage-associated molecular patterns and their dysregulation in the airways

It recently became apparent that some endogenous intracellular and/or extracellular matrix (ECM) components from the host can be released into the extracellular space, subsequently gaining pro-inflammatory functions contrasting with their regulatory functions during normal physiology. In analogy to pathogen-associated molecular patterns ("PAMPs") originating from the outside, these host-self molecules are collectively classified as damage-associated molecular patterns ("DAMPs") [72]. DAMPs often execute their effect *via* activation of one or more TLR(s), but also *via* other members of the pattern recognition receptor family including "scavenger receptors" (*e.g.* CD36) and/or specialised receptors such as RAGE (receptor for advanced glycation end-products) [73].

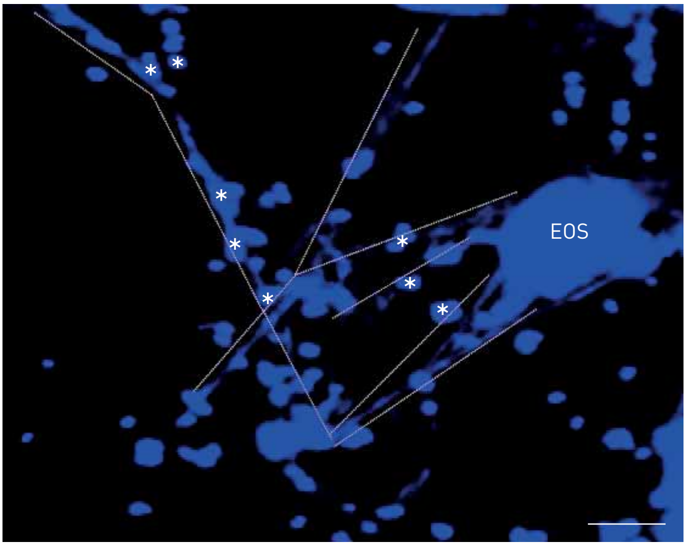

Figure 2. Eosinophil extracellular trap (EET) formation upon *Staphylococcus aureus* exposure. DNA stain with 4′,6-diamidino-2-phenylindole showing an eosinophil (EOS) from a patient with CRS with nasal polyps responding with massive EET formation (indicated by dashed lines) to *S. aureus* (some bacteria are indicated asterisks) *in vitro*. Scale bar: 5 μm.

β-defensins are a group of molecules possessing the characteristics of DAMPs. They are small antimicrobial peptides produced in response to microbial infection of mucosal tissues and skin [74], and may also modulate the functional responses of inflammatory cells. Indeed, β-defensin-2 is reported to activate dendritic cells *via* binding to TLR4 [75]; similarly, β-defensin-3 can activate professional antigen-presenting dendritic cells and monocytes by interacting with TLR1 and TLR2 [76]. Cultured sino-nasal epithelial cells show decreased expression of β-defensin-2 compared with control subjects [77]. These levels were further reduced in the presence of the Th2 cytokines IL-4 or IL-13, while the TLR9 ligand CpG DNA increased the levels of β-defensin-2 after the upregulation of TLR9 expression by the Th1 cytokine IFN-γ. The low β-defensin-2 levels in nasal polyp tissues are therefore in agreement with CRSwNP being a Th2-skewed disease for which reduced [78] or absent [79] expression of TLR9 was reported. Reduced levels of β-defensin-2 and -3 would result in reduced antimicrobial activity against known pathogens such as *S. aureus* [80] which play an important role in the pathophysiology of CRSwNP.

The calcium-binding proteins S100A7 (psoriasin), S100A8 (MRP8 or calgranulin A) and S100A9 (MRP14 or calgranulin B), and heterodimeric form S100A8/A9 (calprotectin), are reported to have antimicrobial effects [81–83]. S100 proteins also show the typical activities of DAMPs when released to the extracellular milieu; they activate TLR4 [84, 85] and RAGE [86]. The inflammatory and remodelling characteristics allow increased retention of S100A8, S100A9 and S100A8/A9 proteins in the ECM. Upon release, the S100 proteins act as a local danger signal inducing inflammatory mediators, predominantly *via* TLR4 activation [84].

Similar to the lungs [87], RAGE is expressed in the upper airways under normal physiological conditions, but dysregulated in chronic inflammatory conditions; in CRSwNP, both tissue-soluble sRAGE and membrane-bound mRAGE protein levels are reduced [88]. Reduced levels of mRAGE protein are associated with an increased proteolytic cleavage of the full-length mRAGE protein which is converted to sRAGE. An imbalance between matrix metalloproteinases and their natural tissue inhibitors of metalloproteinases (TIMPs) was previously reported to occur in CRSwNP [89], resulting in increased proteolytic cleavage. Finally, an increased colonisation rate of *S. aureus* in the airways [90] may further contribute to the overall reduction in sRAGE, as *S. aureus* induces the release of sRAGE from the ECM [88]. High levels of ECP will break non-ECM associated sRAGE down, further reducing the levels. As RAGE is involved in the differentiation of T-cells towards a Th1 phenotype, and RAGE deficiency decreases production of Th1 cytokines while increasing the production of Th2 cytokines [91], its deficit will prevent the redirection of Th cells into the Th1 type. This has been confirmed in *ex vivo* experiments showing that treatment with recombinant sRAGE significantly increased the release of IL-1β and TNF-α, but decreased the levels of IL-5 in type 2-biased tissue [84].

Epithelial barrier function and its impairment in Th2 inflammation

Epithelial cells lining the airway mucosa form not only a physical and chemical barrier to the outside world, but also function as an interface between innate and adaptive immune responses to the abundant particles, microbes, viruses and allergens that are inhaled throughout life.

In conjunction with submucosal glands, the secretory goblet cells produce mucus, a fluid containing hydrated gel-forming mucins, and a range of host defence and cytoprotective molecules, including antimicrobial molecules, antiproteases and antioxidants that act as a "chemical" barrier [92]. The properties of the mucus are dictated in large part by the oligomeric secreted mucins MUC5AC and MUC5B, multifunctional glycoproteins that provide the structural framework of the mucous barrier [93]. The mucus traps and inactivates inhaled agents and facilitates their clearance *via* the mucociliary escalator. It is a testament to the effectiveness of the chemical and physical barriers of the bronchial epithelium that most environmental challenges are largely overcome without the need to develop an inflammatory response. This is well illustrated in recent studies on the importance of MUC5B for defending the airways and for maintaining immune homeostasis. MUC5B deficiency caused accumulation of materials in the upper and lower airways, and led to chronic infection by multiple bacterial species, including *S. aureus*, and to inflammation that failed to resolve normally [94]. An impaired mucociliary clearance is reported in both CRSwNP and allergic rhinitis, and might cause an accumulation of antigens contributing to inflammation [95]. This impairment is mostly acquired as a result of inflammatory or environmental stimuli such as allergens and microbial products [95].

The function of the respiratory mucosa barrier is largely regulated by the apical junctional complex between neighbouring epithelial cells. Apical junctional complexes consist of tight and adherens junctions, and link to the cellular cytoskeleton *via* numerous adaptor proteins [96]. Accumulating evidence indicates that epithelial permeability or barrier dysfunction is a hallmark of airway inflammation and mucosal immunity. Leaky epithelium may result in greater penetration of inhaled allergens, bacteria and viruses in the subepithelial space, facilitating antigen uptake and activating epithelial signal transduction and innate and adaptive immune responses. Inflammatory cytokines are known to disrupt barrier function and apical junctional complexes in intestinal epithelial cells. For example, Th1 (IFN-γ), Th2 (IL-13) and innate immune (TNF-α) cytokines can disrupt the structure and function of intestinal epithelial apical junctional complexes *via* distinct mechanisms [97]. IL-4 disrupts the airway epithelial barrier by altering the normal structure of epithelial adherens junctions and tight junctions *via* mechanisms not involving changes in junction protein expression [98]. CRSwNP patients have a defective epithelial barrier mainly caused by secreted pro-inflammatory cytokines, such as IFN-γ, IL-4 and oncostatin M [99].

Allergens such as HDM, pollen grains and fungi with cysteine proteinase activity, but likely also staphylococcal proteins with enzymatic activity, can degrade occludin and directly disrupt tight junction integrity [100]. Endogenous protease inhibitors cystatin A and SPINK5 (serine peptidase inhibitor, Kazal type 5) have been shown in nasal and bronchial epithelial cells; they serve to protect the airway epithelium from exogenous proteases [101]. Compared with controls and patients with noneosinophilic CRS, patients with eosinophilic CRS showed significantly lower protein and mRNA expression of cystatin A and SPINK5 in the nasal epithelium. Allergen-induced production of IL-25, IL-33 and TSLP in normal human bronchial epithelial cells, favouring type 2 inflammation, was inhibited by treatment with recombinant cystatin A or SPINK5, preventing the protease activity of the allergens [101].

The response of the nasal epithelium to bacteria and viruses has been described to be impaired, inducing inadequate cytokine and IFN release [102], and allowing the invasion of pathogens into the subepithelial space. When healthy mucosa is exposed to frequent viral intruders such as human rhinovirus or herpes simplex virus, a rigorous response from the epithelium with release of IFN-γ and IL-17 can be expected within 24–72 h. However, in a Th2-biased disease such as CRSwNP, this response is largely lacking; instead, significantly more pro-inflammatory cytokines, including IL-1β and TNF-α, are released [102]. These findings were associated with a significantly higher viral invasion at 48 and 72 h in CRSwNP compared with healthy mucosa, indicating a functional deficit in the defence against viruses. IL-4 and IL-13, through inhibition of TLR3 expression and signalling (IFN-responsive factor 3), may impair this immune response to viral infection [103]. IL-4 and IL-13 were induced by rhinovirus in the asthmatic airway *in vivo* and relate to exacerbation severity; this induction was entirely dependent on IL-33 release from epithelial cells [104]. IL-4- and IL-13-induced barrier dysfunction was accompanied by reduced expression of membrane apical junctional complex components. This study indicates that IL-4 and IL-13 have disruptive effects on airway epithelial barrier function. Th2 cytokine-induced epithelial barrier dysfunction may contribute to airway inflammation in allergic asthma.

Also impacted by Th2 cytokines, macrophages are alternatively activated, which renders them inadequate to phagocytose and kill bacteria, once invaded into the mucosa [105]. Bacteria are frequently cultured from samples of severe asthma patients, suggesting a defect in bacterial clearance from the airway. Persistence of bacteria in the lower airway may result partly from a reduced phagocytic capacity of macrophages for bacteria [17]. Macrophages produce a variety of cytokines and mediators that are vital for immune and inflammatory responses against external agents. It has been shown that there was a reduction in phagocytosis of *Haemophilus influenzae* and *S. aureus* by monocyte-derived macrophages from patients with severe asthma [104]. We found a significantly lower percentage of phagocytosis of *S. aureus* by CD206$^+$ cells in CRSwNP compared with control inferior turbinate tissue. The clearance of nonopsonised bacteria by macrophages depends on their innate immune receptors for detection, binding and internalisation of pathogens [105]. In summary, we propose that the increased presence of *S. aureus* and other microorganisms in CRSwNP can be partly explained by inefficiency of the phagocytic system in the sino-mucosal tissue of these patients. In line with our study, defects in phagocytosis of bacteria and apoptotic cells and increased bacterial colonisation have been described for several lower airway pathologies, including asthma, CF and COPD [106].

The relationships between the upper/lower airway microbiome, acute infection and exacerbation in chronic respiratory disorders are discussed further by Xepapadaki *et al.* [107] elsewhere in this *ERS Monograph*.

Conclusions

In the majority of patients, inflammation in the upper and lower airways is characterised by a type 2 inflammation. Presence of this type of inflammation increases the risk for comorbidity in the other parts of the airways. Severe inflammatory disease also occurs in both airways, with the expression of SE-IgE as a hallmark. There is accumulating evidence that SE-IgE antibodies can be used as a biomarker for severe airway disease. It is yet to be clarified whether *S. aureus* profits from the type 2 inflammation and its consequences, such as impairment of the epithelial barrier, innate and adaptive immunity, and secondarily modifies a pre-existing inflammation, aggravating the disease, or whether it may be causal in inducing an inflammation leading to disease under certain circumstances. It is clear that *S. aureus* can reside intramucosally, releasing secreted proteins into the mucosa, and by this regulates Th2 cytokines. It also is clear that eosinophils in airway disease do have a job to do defending the airways against microorganism such as *S. aureus* by EETs, apparently after other defence mechanisms have failed. Type 2 inflammation, impairment of epithelial defence mechanisms, eosinophils and EETs, and finally *S. aureus* and its products unite the airways in disease. It remains to be clarified which targets are optimal to treat severe airway disease: the restoration of the epithelial barrier and immune defence, the suppression of adaptive immune regulators such as IL-5, IL-4, IL-13 or IgE and eosinophils, the microorganism and its products, or a combination thereof. Antibiotics, oral glucocorticosteroids, anti-IgE and anti-IL-5/IL-4 receptor α approaches have all been demonstrated to be effective in upper and lower airway diseases [108, 109].

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Chapter 9

The nose and sinuses in COPD

John R. Hurst[1] and Arturo Huerta Garcia[2]

COPD is associated with nasal symptoms, inflammation and airway narrowing which persists after smoking cessation. This is not recognised in current COPD guidelines. Nasal symptoms and inflammation are increased at exacerbation, and there is some evidence that the magnitude of the inflammatory responses in the upper and lower airways is similar. Nasal symptoms, which associate with inflammation, cause impairment to QoL and may predispose to increased risk of upper airway viral infection. Potential mechanisms of interaction include loss of the air-conditioning function of the nose, unified airway inflammatory cell "homing", sino-bronchial reflexes and post-nasal drip. The upper airway does not appear to be an adequate surrogate for studying the lower airway in COPD. While symptoms cause QoL impairment and therefore warrant treatment of themselves, whether nasal treatment can improve lower airway outcomes has been inadequately researched and specific intervention on nasal inflammation in COPD poorly studied. This remains a major evidence gap. This chapter considers the evidence for sino-nasal involvement in COPD.

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When a genetically susceptible individual is exposed to sufficient environmental stimulus (typically cigarette smoke in the developed world and/or biomass indoor air pollution in low- and middle-income countries) the end result is a spectrum of coexisting lung conditions. Alveolar destruction is termed emphysema, a pathological diagnosis. Irritation and inflammation of the large airways with cough and mucus production results in the clinical diagnosis of chronic bronchitis. COPD is diagnosed when there is evidence of small airway airflow obstruction on spirometry, and COPD is therefore a physiological diagnosis. The 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) document [1] defines COPD as "a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases". Given that the upper and lower airways are genetically identical, and that the environmental exposure in the lung must, at least in part, have passed through the

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upper airway it is plausible that there may be upper (sino-nasal) involvement in COPD. What is the evidence to support this suggestion?

There are few studies that have adopted the idealised design of comparing a random selection of a population with spirometrically confirmed COPD to age- and smoking-matched control subjects without COPD. Most of the published studies either utilise large epidemiological databases where COPD has not necessarily be confirmed or report on small cohorts of patients with confirmed COPD known to the researchers. We will not review the literature on the effect of cigarette smoke on the upper airway (this has been systematically reviewed elsewhere [2]), but when considering the studies below it is important to differentiate the effect of active smoking from effects associated with COPD (which therefore persist after smoking cessation). Note that most cigarette smoke bypasses the nose and reaches the lung *via* the mouth. However, the nasal airway may be exposed to a proportion of side-stream smoke (which originates from the tip of the cigarette) and a proportion of smokers exhale smoke through the nose. In brief, both active and second-hand cigarette smoke are associated with symptoms of CRS, and clinical and *in vitro* studies demonstrate that cigarette smoke is toxic to the nasal epithelium, resulting in reduced mucociliary clearance and increased airway resistance (reviewed in [2]). It is also important to remark that the terminology used to describe upper airway involvement varies between studies. So what is the evidence that COPD is associated with upper airway symptoms and that these are important? In the sections below we present a narrative review, highlighting the studies that we consider most important. This is not a formal systematic review.

Upper airway symptoms in COPD

A number of large epidemiological studies have reported associations between self-reported diagnoses of COPD and CRS. The largest, reporting associations in over 73 000 subjects [3], concluded that rhinosinusitis was between three and four times more prevalent in subjects self-reporting chronic bronchitis or emphysema. This relationship was independent of age, sex, socioeconomic status and total tobacco exposure. The use of self-reported upper and lower airway disease is a limitation, but a necessary consequence of studies that employ large databases. The findings are similar to those of Montnemery *et al.* [4], who were the first to attempt this type of study in 2001. In their analysis, 40% of an 8469-strong Swedish population self-reporting COPD also reported chronic nasal symptoms *versus* 33% of people without COPD. In a follow-up to the original study, Nihlén *et al.* [5] examined how reports of symptoms tracked with the future incidence of chronic bronchitis and/or COPD. Thick, yellow nasal discharge and nasal blockage, or nasal symptoms induced by exposure to damp or cold air and tobacco smoke, at baseline all predicted an increased incidence of chronic bronchitis and/or COPD. A database study from Taiwan including 34 029 subjects and a similar number of controls demonstrated an increased risk of CRS without nasal polyps in the subjects with COPD (hazard ratio 3.24, 95% CI 2.65–3.96; $p<0.01$) [6].

Let us now consider the studies examining the presence of upper airway involvement in people with confirmed COPD, which are much smaller in scale. Roberts *et al.* [7] provided the first report, in 2002. The prevalence of nasal symptoms in a cohort of 61 patients with moderate and severe airflow obstruction was 75%, most commonly rhinorrhoea. The finding from this study that symptoms were not more common in current compared with ex-smokers is important in that it suggests upper airway manifestations of COPD persist even after smoking cessation. In a follow-up analysis, researchers from the London COPD cohort studied how nasal symptoms change with time [8]. This analysis reported that the odds ratio (OR) for nasal discharge increased by 1.32% (95% CI 1.19–1.45%; $p<0.001$) per year, the OR for sneezing increased by 1.16% (95% CI 1.05–1.29%; $p=0.005$) per year, the OR for post-nasal drip increased by 1.18% (95% CI 1.03–1.36%; $p=0.016$) per year and the OR for anosmia increased by 1.19% (95% CI 1.03–1.37%; $p=0.015$) per year. In addition, nasal discharge was more likely to be present in patients susceptible to frequent exacerbations (OR 1.96, 95% CI 1.17–3.28; $p=0.011$).

A smaller study by Hens *et al.* [9] was notable for including 24 age- and smoking-similar controls with the 31 current and ex-smoking COPD patients. A visual analogue scale score for nasal obstruction and discharge (but not nasal "itch" or sneezing) was greater in the COPD patients than the controls.

The largest of the studies in people with confirmed COPD is a French cohort examining nasal symptoms in 274 subjects (median FEV_1 48% predicted) [10]. The prevalence of chronic nasal symptoms was 42% (most commonly rhinorrhoea and nasal obstruction), and the presence of chronic nasal symptoms tracked with both health status impairment and breathlessness, but not exacerbations. Cumulative smoking and atopy both increased the risk of nasal symptoms. The relationship between nasal symptoms and health status implies that such symptoms should be taken seriously. As COPD is generally dominated by lower respiratory symptoms, upper airway symptoms may not be sufficiently identified and mitigated in current approaches to COPD care. The Sino-Nasal Outcome Test (SNOT) questionnaire was developed to assess outcomes following surgery for rhinosinusitis, but provides a QoL score for chronic upper airway symptoms that has, to some extent, been validated. In 65 patients with COPD, the SNOT score was higher than that reported in controls and correlated with the number of nasal symptoms present [7]. There was a poor correlation between the SNOT score and the St George's Respiratory Questionnaire, which is commonly used to assess health status in COPD, suggesting that the two questionnaires may be measuring different aspects of COPD health status burden [7].

Further evidence of the potential importance of sino-nasal involvement in COPD derives from an analysis of factors determining "treatment failure" following 232 exacerbations in 107 patients [11]. A history of sinusitis was significantly associated with the need for a physician visit with persistent symptoms and change in antibiotics.

Approaching relationships between upper and lower airway disease from the ENT perspective, Ragab *et al.* [12, 13] report in two studies that 60% of a small sample of patients with CRS were found to have lower airway symptoms or spirometric abnormalities and that patients who had asymptomatic airflow obstruction had a higher proportion of neutrophils in sinus washings than those with normal spirometry.

Not all studies find an increased prevalence of nasal symptoms in COPD. However, in summary, nasal symptoms are frequent in cigarette smoke-induced COPD, cause impairment to QoL and persist after smoking cessation. We are not aware of any papers examining upper airway symptoms in biomass-induced COPD, in which nasal exposure to irritant may be greater. Given that lower airway symptoms in COPD relate to airway inflammation, this raises the question that there may be upper airway inflammation in COPD. What is the evidence for this?

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Upper airway inflammation in COPD

A number of studies have reported on upper airway inflammation in COPD. Again, none have approached the ideal study that might compare upper and lower airway samples from the same patient, with smoking-matched controls, with adequate statistical power. Various different approaches to sampling the upper airway have been employed, including assessment of soluble mediators from absorption or samples such as nasal lavage and the assessment of nasal biopsies. The repeatability and validity of assessing soluble markers in nasal wash and absorption specimens has been poorly examined. Biopsy studies are open to the criticism that inflammatory changes may not be uniform and therefore that samples may not be representative. An alternative way of assessing inflammation is with direct visualisation of the airway at nasendoscopy or through imaging studies such as sinus CT.

The most important of the biopsy studies, which included control patients, was the VACHIER *et al.* [14] study of 2004. Active smoking was associated with squamous metaplasia and infiltration of the nasal and bronchial mucosa with $CD8^+$ cells compared with nonsmokers, but there were also differences between the smokers with and without COPD. The number of eosinophils was lower in COPD, while neutrophils and macrophages were more abundant in smokers with COPD, suggesting that COPD is associated with further increases in nasal inflammation over that due to smoking alone.

NIHLÉN *et al.* [15] provided the first report of nasal airway inflammation in COPD, in 2003. 26 control and 23 subjects with COPD had nasal lavage before and after nasal histamine challenge. While there were not statistically significant differences in the concentrations of nasal inflammatory markers between the two groups at baseline, histamine challenge resulted in a more pronounced nasal neutrophil response in subjects with COPD compared with controls, which was greatest in the COPD subjects with nasal symptoms. Importantly, both groups contained current and ex-smokers. HURST *et al.* [16], in 2005, included a smoking-similar control group, and was the first to compare nasal and lower airway inflammation in the fluid phase. This study suggested that nasal inflammation persists in COPD following smoking cessation (as it does in the lower airway), that the magnitude of the inflammatory response in the upper and lower airways is similar (there was a significant correlation between nasal wash and sputum IL-8 concentration), and that subjects with potentially pathogenic bacteria in sputum had both a higher nasal bacterial load and more frequently reported post-nasal drip. It is important to note that this study was conducted in the “pre-microbiome” era.

What of the studies that have tried to image nasal involvement in COPD? HENS *et al.* [9] reported nasal endoscopic appearances (and inflammation) in COPD patients and age- and smoking-similar controls. A composite nasal endoscopy score comprising nasal congestion, secretions and polyps was significantly higher in the COPD patients than the controls. Regarding inflammation, COPD patients had higher nasal levels of eotaxin, granulocyte −macrophage colony-stimulating factor and IFN-γ than controls. The eotaxin result was confirmed in a small study of 19 COPD patients in which eotaxin-1 concentration was higher in nasal brushings from patients with COPD compared with controls [17]. Other eotaxins were not present at statistically different concentrations and there is a risk with small studies of publication bias, and both type 1 and type 2 errors. A second small study also suggested increased nasal endoscopic abnormalities compared with controls, but interpretation of the results presented in this paper, including the assessment of CT, is challenging [18].

Cigarette smoke might impair nasal mucosal clearance and Ito *et al.* [19] report a comparison of 93 subjects: 23 ex-smokers with COPD, 17 smokers with COPD, 27 current smokers with and without COPD, and 26 nonsmokers. The saccharin transit time (STT) was used to assess mucociliary clearance. STT in smokers with and without COPD was similar, and longer (therefore impaired) than that seen in ex-smokers with COPD and healthy controls, with and STT in the latter two groups also being similar. These results suggest smoking rather than COPD affects STT and that smoking cessation can improve nasal mucociliary clearance. This is at variance with an older study reporting impaired nasal mucociliary clearance in ex-smokers with COPD compared with controls [20]. In this study, ciliary beat frequency was also reduced and in a second study, enrolling a mixed group of patients with COPD smokers and ex-smokers, in whom ciliary beat frequency was reduced compared with controls, this could be increased *ex vivo* with pharmacological agents commonly used to treat COPD, including long-acting β-agonists and long-acting anti-muscarinic drugs [21]. Whether such effects are clinically relevant remains to be determined.

Taken together, these studies suggest inflammatory nasal airway involvement in COPD compared with control subjects, which persists after smoking cessation, and the potential for relationships between the upper and lower airways. The latter point has implications in being able to use the upper airway as a more accessible model of the lower airway and raises the possibility that modulation of upper airway inflammation may affect lower airway outcomes. These are both discussed further later in this chapter.

Nasal airway obstruction in COPD

As COPD is defined by the presence of inflammatory airflow obstruction in the lung, the question arises as to whether sino-nasal involvement in COPD results in nasal airway obstruction. Airway obstruction in the nose is predominantly mediated by engorgement of venous sinusoids, in comparison to the lung where smooth muscle tone, thickening of the airway wall and excess mucus are major contributors.

Hurst *et al.* [22] assessed nasal airway obstruction in COPD using acoustic rhinometry, a technique that measures nasal airway cross-sectional area as a function of distance into the nose. The portion of the nasal airway most susceptible to inflammatory obstruction through engorgement of the sinusoids is referred to as the second minimum cross-sectional area (MCA2) and this was significantly narrower in patients with COPD experiencing chronic nasal symptoms compared with those without such symptoms [22]. The authors also reported a significant relationship between the severity of nasal airway and pulmonary airflow obstruction [22].

Upper airway involvement during COPD exacerbations

Much of the morbidity, mortality and therefore healthcare costs in COPD are associated with periodic deteriorations in respiratory health, termed “exacerbations”. The 2017 GOLD document defines an exacerbation as “an acute worsening of respiratory symptoms that result in additional therapy" [1]. Some patients ("frequent exacerbators") are more susceptible to exacerbation [23], and those affected have accelerated decline in lung function [24], poorer QoL [25] and increased mortality [26]. Most exacerbations are caused by airway infection: acquisition of respiratory viruses and/or alterations in the airway bacterial microbiome. Given that respiratory viruses often affect the upper airway too, it is plausible that there may be a role for the upper airway in exacerbation of COPD.

The London COPD cohort group reported that at the time of exacerbation, nasal discharge was increased for an average of 7 days, and blocked nose, sneezing and post-nasal drip increased for an average of 3 days [8]. Working with the same group, Hurst *et al.* [27] reported an elevation in nasal wash inflammatory markers at exacerbation compared with baseline, with nasal wash inflammation relating to symptom burden and IL-6 concentration higher in exacerbations associated with isolation of rhinovirus. Rhinovirus is the major cause of COPD exacerbations and patients susceptible to frequent exacerbations appear more susceptible to acquiring colds [28].

The most robust evidence regarding nasal symptoms during rhinovirus exacerbations of COPD is derived from studies using experimental rhinovirus infection [29]. As illustrated in figure 1, a composite upper respiratory tract symptom score was higher in the COPD than a control population and increased above baseline for 2–14 days post-inoculation in the COPD group compared with 1–12 days in the control subjects. The nasal symptoms preceded the elevation in lower respiratory symptoms in the COPD subjects, which were above baseline over days 5–19. Comparing the virological responses, rhinovirus load was maximal at 4–8 days post-inoculation in nasal lavage compared with day 5 in sputum and the nasal lavage viral load was 1–2 log units greater in the COPD group compared with the controls (figure 2). The inoculum required to induce symptoms in COPD was less than that in control subjects and it is tempting to speculate that this reflects pre-existing

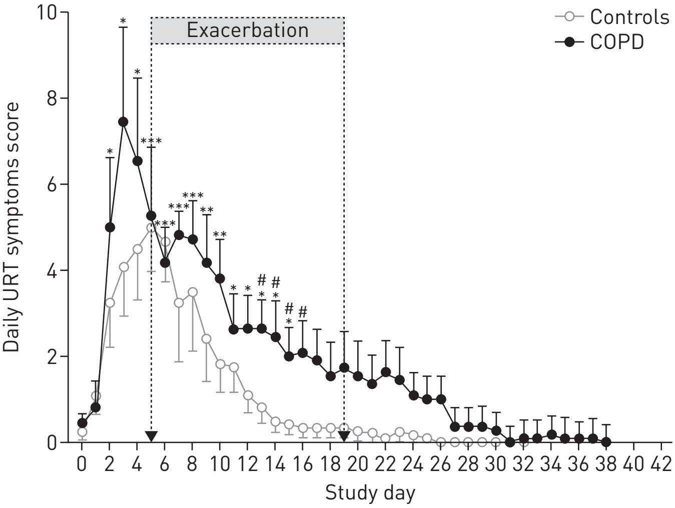

Figure 1. Time course of a composite upper respiratory tract (URT) symptoms score following experimental rhinovirus inoculation in control *versus* COPD subjects. For comparison, the total lower respiratory symptom scores in the COPD patients was increased over baseline (BL) on days 5–19 ("Exacerbation"). *: $p<0.05$ *versus* BL; **: $p<0.01$ *versus* BL; ***: $p<0.001$ *versus* BL; $^{\#}$: $p<0.05$, patients with COPD *versus* control. Reproduced and modified from [29] with permission from the publisher.

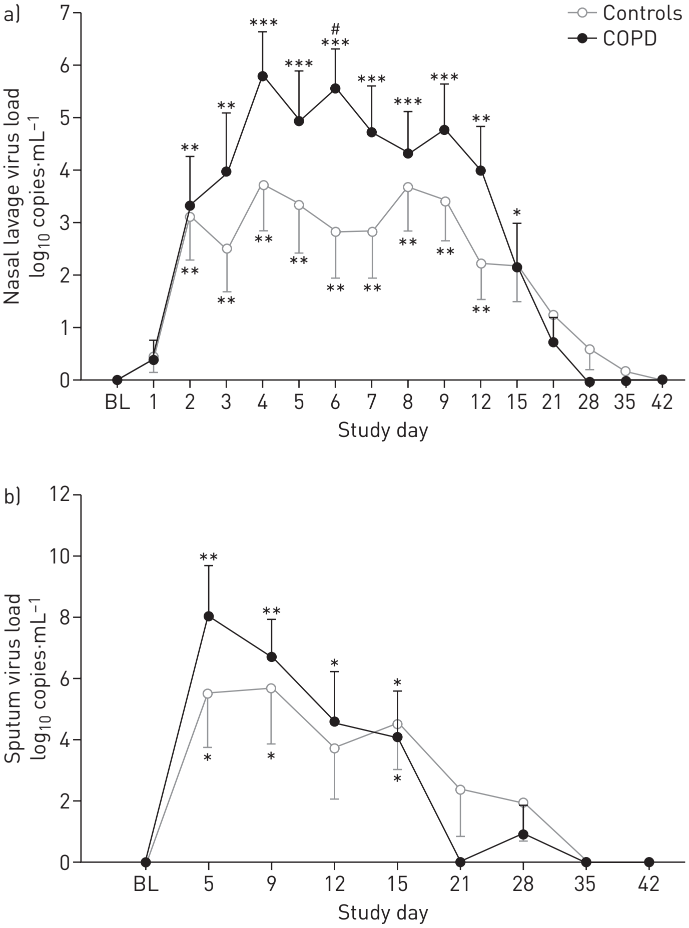

Figure 2. Time course of rhinovirus load (quantitative polymerase chain reaction) in a) nasal lavage and b) sputum following experimental infection in control subjects and those with COPD. BL: baseline. Data are presented as mean±SEM. *: $p<0.05$ *versus* BL; **: $p<0.01$ *versus* BL; ***: $p<0.001$ *versus* BL; $^{\#}$: $p<0.05$, patients with COPD *versus* control. Reproduced and modified from [29] with permission from the publisher.

upregulation of inflammation in the subjects with COPD. Pilot work from the same group had reported increases in nasal inflammatory markers in association with experimental rhinovirus infection [30]. The relationships between the upper/lower airway microbiome, acute infection and exacerbation in chronic respiratory disorders are discussed further by Xepapadaki *et al.* [31] elsewhere in this *ERS Monograph*.

Does nasal intervention improve outcomes in COPD?

Intervention in the nose might beneficially reduce nasal symptoms, but also, by improving the function of the nose, potentially benefit lower airway outcomes too. While an attractive hypothesis, we are aware of only one small nasal intervention study, which at best provides a proof of concept and not a definitive result. Callebaut *et al.* [32] reported a pilot study in which 27 patients completed a 12-week double-blind randomised trial using fluticasone furoate (110 µg daily), with final assessment at 16 weeks. Patients were stable on inhaled corticosteroid and long-acting β-agonist. Patients randomised to nasal fluticasone furoate reported reduced nasal blockage, post-nasal drip and nasal discharge after 6 weeks treatment, and a reduction in cough. In a “responder” analysis, there was a significant decrease in nasal IL-8 concentration (but not other markers) in the nine out of 14 patients in the fluticasone furoate group reporting partial or complete relief of nasal symptoms.

Mechanisms of interaction between the upper and lower airways

The data presented thus far support the concept that COPD is associated with nasal symptoms and inflammation that persists after smoking cessation, the magnitude of which reflects that occurring in the lower airway. Nasal symptoms and inflammation are increased still further at exacerbation. The important question remains as to whether this represents coexistent disease or whether the presence of inflammation at one site can influence clinical manifestations at the other.

There are a number of mechanisms through which upper airway involvement might affect the lower airway. Nasal dysfunction permits cold, dry and unfiltered air to access the lung. Work in asthma/rhinitis in which lower airway stimulation results in nasal inflammation and nasal stimulation results in lower airway inflammation supports the concept of inflammatory cell homing to the whole airway following stimulation at any part of it [33, 34]. Neuronal naso-bronchial reflexes have also been proposed [35]. Finally, it is possible that through mechanisms such as post-nasal drip, upper airway inflammatory mediators and bacteria may access the lower airway directly.

Other applications of nasal involvement in COPD

Studies reporting relationships between the upper and lower airways in COPD raise the attractive hypothesis that the nose, and samples from the nose, may be used as a more readily accessible surrogate for lower airway sampling in mechanistic and interventional studies. However, while initial data suggested that nasal and bronchial epithelial morphology was similar [36], more recent data suggest that matched nasal and bronchial epithelial cells behave dissimilarly in response to inflammatory stimulation *ex vivo* [37].

Clinical practice and evidence gaps

Based on current evidence, our suggested approach to the clinical management of nasal symptoms is to ask about their presence and to manage them using appropriate guidance for the management of CRS. At present, there is insufficient evidence to recommend treating the upper airway to improve lower airway outcomes and therapeutic intervention on sino-nasal involvement in COPD remains a major evidence gap. International guidelines should acknowledge the existence of upper airway involvement and symptoms in COPD. ENT clinicians should be alert to the possibility of occult COPD in patients with CRS.

Conclusions

COPD is associated with nasal symptoms, inflammation and airway narrowing which persists after smoking cessation. This is not recognised in current COPD guidelines.

Symptoms and inflammation are increased at exacerbation, and there is some evidence that the magnitude of the inflammatory responses in the upper and lower airways is similar. Nasal symptoms, which associate with inflammation, cause impairment to QoL and may predispose to increased risk of upper airway infection. Potential mechanisms of interaction include loss of the air-conditioning function of the nose, unified airway inflammatory cell "homing", sino-bronchial reflexes and post-nasal drip. The upper airway does not appear to be an adequate surrogate for studying the lower airway in COPD. While symptoms clearly cause QoL impairment and therefore warrant treatment of themselves, whether treatment can improve lower airway outcomes has been inadequately researched and specific intervention on nasal inflammation in COPD poorly studied. This remains a major evidence gap.

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Chapter 10

Chronic rhinosinusitis in non-cystic fibrosis bronchiectasis and primary ciliary dyskinesia

Johanna Raidt and Claudius Werner

CRS is a common disease often associated with different medical disorders, including rare mucopurulent respiratory disorders such as CF, non-CF bronchiectasis and PCD. CRS is present in the majority of patients with non-CF bronchiectasis. Individuals with non-CF bronchiectasis and CRS suffer from more severe lung disease than individuals with non-CF bronchiectasis alone. PCD patients show persistent rhinitis from birth and CRS as a hallmark symptom from adulthood. CRS may be accompanied by nasal polyps, especially in PCD subjects. Therapeutic approaches in CRS are focused on conservative management, mainly nasal (saline) irrigation. Topical corticosteroids should be considered if nasal polyps are present. In PCD, however, the benefit of topical corticosteroids is controversial due to a potentially increased risk of infection. Sino-nasal surgery should be performed with caution.

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Rhinosinusitis is defined as simultaneous mucosal inflammation of the paranasal sinuses and the nose. The acute form (ARS) occurs suddenly, lasts <12 weeks and is characterised by at least two of the following symptoms: nasal blockage, obstruction or congestion, nasal discharge (anterior/posterior nasal drip), facial pain or pressure, and reduction or loss of smell [1]. In the chronic form (CRS), symptoms persist for ⩾12 weeks. CRS may be complicated by nasal polyps, which must be confirmed *via* endoscopy.

CRS may occur as an isolated disorder (*e.g.* caused by anatomical abnormalities) or as part of a multisystemic disease [1, 2]. Allergy is a very common cause of CRS in both adults and children [1], and directive diagnostic testing should be initiated accordingly. CRS also is a hallmark symptom of rare mucopurulent respiratory disorders such as CF, non-CF bronchiectasis and PCD.

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Initially described by Laennec in 1819, non-CF bronchiectasis represents a set of different lung diseases with permanent dilatation of the bronchi [3]. Non-CF bronchiectasis is diagnosed after exclusion of specific disorders such as immunodeficiencies, α_1-antitrypsin deficiency, CF, PCD and others. Underlying conditions can be inherited or acquired, but numerous cases remain unsolved [4]. CRS may be associated with non-CF bronchiectasis, but is not necessarily present in all affected individuals [5]. Patients with non-CF bronchiectasis suffer from chronic productive cough and recurrent respiratory tract infections. Bronchiectasis can be identified by high-resolution CT (HRCT) [4] and is classified as focal or diffuse, and as cylindrical, varicose or saccular.

The term PCD describes a heterogeneous group of hereditary disorders characterised by chronic infections of the upper and lower airways, organ laterality defects and fertility problems. As early as 1933, the triad of bronchiectasis, CRS and visceral situs inversus totalis had been described by Kartagener [6]. In 1976, Afzelius reported that PCD is caused by defective motile cilia [7]. Subsequent research elucidated that most PCD variants also affect the motile cilia of the embryonic node, which results in a randomisation of the left–right distribution of the visceral organs. Thus, organ laterality defects occur in ~50% of PCD cases (usually situs inversus totalis, which is then referred to as "Kartagener's syndrome"), whereas ~50% of patients display a situs solitus [8]. Newborns with PCD show persistent rhinitis or nasal blockage, which leads to feeding difficulties. Following development of the paranasal sinuses, children develop CRS, which lasts through adulthood and is present in 100% of adult PCD patients [8–12].

The purpose of this chapter is to highlight CRS in non-CF bronchiectasis and PCD. Rhinosinusitis of differing aetiology (*e.g.* CF, asthma and COPD) is discussed in other chapters throughout this *ERS Monograph* [13].

Epidemiology

CRS is a frequently occurring disease and causes considerable costs for the healthcare system [12, 14, 15], with significant impacts on QoL and general health [16, 17]. As CRS shows great variety in clinical presentation, patients often consult numerous clinical disciplines, such as pulmonologists, allergists, otolaryngologists, paediatricians, primary care and emergency physicians. A survey in the USA showed that 14% of the more than 200 000 participants had had sinusitis diagnosed by a doctor or healthcare professional during their lifetime [18]. In Canada, CRS diagnosed by healthcare professionals had a prevalence of 3.4% in male and 5.7% in female individuals [19]. Recently, a study estimating the prevalence of CRS in Europe using the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 (EP^{3}OS) criteria [20] was performed in 19 centres in 12 European countries and encompassed over 50 000 respondents [21]. It showed an overall prevalence of CRS of 10.9% with a remarkable geographical variation range (6.9% in Brandenburg, Germany, to 27.1% in Coimbra, Portugal) and an association with smoking.

In recent decades, medical progress has led to a reduction in the prevalence of acquired forms of bronchiectasis, mainly by successful antibiotic treatment of chest infections. However, nonsymptomatic bronchiectasis is increasingly being detected by chance using advanced imaging techniques. Differences in the use of diagnostic facilities (*e.g.* CT) contribute to high prevalence variability across Europe, as well as differences in risk factors (*e.g.* tuberculosis prevalence) predisposing to non-CF bronchiectasis [22]. UK data report a high prevalence rate of 566 per 100 000 for women [23], while German data show a rate of 67 per 100 000, which might be underestimated [24]. Post-infectious bronchiectasis seems to be more frequent in southern Europe (Greece, Spain and Italy) [22]. CRS is very common in non-CF bronchiectasis [5]. Compared with patients without CRS, patients with non-CF bronchiectasis and CRS have impaired lung function, increased levels of C-reactive protein [5], a lost sense of smell [25, 26] and a reduced QoL [25, 27]. Of note, non-CF bronchiectasis is a diagnosis made after exclusion of other underlying disorders, which in turn are often difficult to diagnose (*e.g.* PCD; see the section on diagnostic approaches later in this chapter). Therefore, it is very likely that a subset of individuals with non-CF bronchiectasis and CRS have an undiagnosed underlying disorder such as PCD or atypical CF.

PCD is a rare genetic disorder and has an estimated prevalence of 1 per 4000 to <1 per 60 000 [28–30]. Exact prevalence is difficult to determine, because there is wide phenotypic variability, and access to state-of-the-art diagnostic testing is not available in many countries. As most variants are inherited as an autosomal recessive trait, PCD prevalence is higher in societies with a high degree of consanguinity [31, 32]. Hence, a PCD diagnosis often is established late or even missed completely [29].

Pathophysiology

The nasal cavity and paranasal sinuses are air-filled spaces that communicate *via* small apertures (ostia). They are lined with a mucosal membrane carrying a ciliated epithelium, which secrets mucus and transports particles and microorganisms towards the nasopharynx where they can be expectorated or swallowed. The nose and paranasal sinuses are not only the first line of defence but also heat and humidify the inhaled air and reduce the weight of the skull. During inflammation and infection, swelling of the mucosa and increased mucus viscosity or production result in a blockage of connecting ostia that inhibits mucus clearance. CRS is defined as inflammation of the nose and paranasal sinus mucosa, due to poorly understood reasons [1]. It is often associated with allergy, bacterial or viral infections, mucociliary dysfunction, problematic anatomical conditions and, in particular, lower airway disease, such as asthma, COPD, PCD and non-CF bronchiectasis [1, 2, 13]. Bacterial biofilms are probably present in all patients with CRS and play a significant role in the pathophysiology of the disease. Biofilms pose a potent source of bacteria and mediators that promote the systemic inflammation in CRS [33].

A subgroup of patients with CRS suffers from nasal polyps [1, 13]. The polyps appear as grape-like structures in the nasal cavity that grow out of the inflamed nasal mucosa. It remains a matter of debate as to why the tissue grows and forms polyps in some patients with CRS [34]. Nasal polyps aggravate the mechanical obstruction present in CRS and therefore further inhibit secretion clearance. A functional consequence is a deterioration of the sense of smell in these patients [1, 35, 36]. Nasal polyps exhibit a high tendency to recur after surgical removal [36].

Individuals with non-CF bronchiectasis suffer from strong inflammation in response to respiratory infection or tissue damage [37]. This leads to further airway damage and bronchial dilatation and impaired mucociliary clearance. Mucus stasis, bacterial colonisation and subsequent endogenous defence mechanisms, such as release of cytokines or neutrophils, maintain the vicious cycle [38–40]. Mucus in non-CF bronchiectasis is always viscous, even in episodes of low disease activity [41]. Development of bronchiectasis is enhanced by chronic mucus retention and plugging. Non-CF bronchiectasis may be limited to the chest, such as in individuals who have experienced a severe lung infection or injury. However, as the upper and lower respiratory tracts are lined with the same ciliated epithelium, microorganisms in bronchiectatic lungs can easily ascend to the upper airways and cause rhinosinusitis [42]. Thus, it is likely that chronic ciliary dysfunction and mucus hypersecretion affect the upper airways in many patients with non-CF bronchiectasis. Once this vicious cycle is established, mucus stasis, ciliary dysfunction and (bacterial) infection mutually stimulate the course of the disease. Clinically, this results in chronic blockage of paranasal ostia by swollen mucosa, which in turn enhances the process of inflammation and tissue damage. Finally, affected individuals suffer from CRS, which has become independent of (bacterial) infection by heavy tissue damage and the ongoing inflammatory response of the host [2, 4, 5, 43].

A forward beating stroke followed by a backward recovery stroke characterises normal ciliary beating. The coordinated activity of neighbouring cilia generates a directed fluid flow [44, 45]. This synchronised activity is essential for mucus transport and mucociliary clearance. In PCD, ciliary beating is severely impaired by defects of the ciliary axoneme [44, 46]. This quickly progresses to epithelial damage, mucus hypersecretion and infection, biofilm formation and chronic inflammation [47]. Motile cilia exhibit a conserved ciliary ultrastructure with a characteristic 9+2 arrangement (figure 1).

The origin of PCD symptoms becomes clear by understanding the distribution and function of motile cilia. Ciliated epithelial cells are present in the upper respiratory tract (nasopharynx, nasal meatus, paranasal sinuses, middle ear and Eustachian tube), in the lower respiratory tract (trachea and bronchi), in the brain ventricles, and in the female and male reproductive systems (Fallopian tubes, cervix, ductuli efferentes of the testis and epididymis) [45, 50, 51]. Ciliary dysfunction in the reproductive system leads to fertility problems [45, 52]. Humans with PCD only rarely suffer from occlusive hydrocephalus internus due to dysfunction of ependymal cilia [51, 53], whereas in other species,

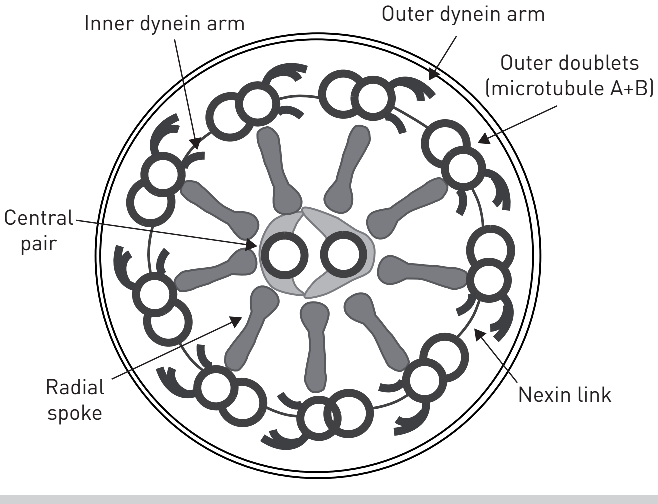

Figure 1. Schematic cross-section of a motile cilium. Nine outer doublets surround a central pair ("9+2"), which is connected to the outer doublets through radial spokes [48]. The outer doublets are linked to each other *via* nexin-linked proteins. Outer and inner dynein arms are responsible for generation and regulation of ciliary beating [49].

hydrocephalus internus is an obligate symptom [54]. Accumulation of mucus and pathogens in the lower airways causes bronchiectasis and ultimately leads to respiratory failure [10, 55, 56]. As mucus and pathogens are not transported towards the nasopharynx from the nasal cavity and the paranasal sinuses, PCD patients develop severe chronic pansinusitis early in life [8–11, 55].

Clinical manifestations

Individuals with CRS experience nasal blockage, obstruction or congestion, nasal discharge, post-nasal drip, facial pain and pressure, and a reduction or even loss of smell. CRS is often accompanied by other respiratory symptoms, such as cough, dysphonia and sore throat, caused by tracheal, pharyngeal and laryngeal irritation [1]. In addition, headache, drowsiness, malaise and episodes of fever are common in CRS. Nasal polyps may cause or worsen nasal congestion and smell disorders [36].

Non-CF bronchiectasis should be suspected in individuals with chronic cough, daily sputum production and recurrent airway infections. Productive cough is the most common symptom in patients with non-CF bronchiectasis. 25% of patients report a very low sputum production during stable health conditions, but experience a significant increase during infectious exacerbations [57, 58]. Chest pain, episodes of fever, shortness of breath and occasionally haemoptysis are further symptoms in individuals with non-CF bronchiectasis [5, 58, 59]. CRS is present in up to 77% of patients with non-CF bronchiectasis [5]. These patients show anterior and posterior rhinorrhoea as well as nasal congestion as major symptoms meeting the EP^{3}OS criteria [1, 5, 20]. Interestingly, lung disease is more severe in individuals with non-CF bronchiectasis and CRS than in subjects with non-CF bronchiectasis alone [5, 60].

The mortality of patients with non-CF bronchiectasis increases with disease duration: the mortality rate is reported to be 2–5% 2 years after diagnosis and increases to 10–30% after 5 years and to 35% after 15 years [22, 61]. Patients with non-CF bronchiectasis show one to three exacerbations per year initially. During the course of the disease, this increases to up to 12 exacerbations per year [22].

Unlike non-CF bronchiectasis, which is diagnosed mainly in adults and only rarely in children, PCD is characterised by upper and lower airways disease from early infancy or even from birth. Directly after birth, 85% of newborns with PCD have an unexplained neonatal respiratory distress syndrome including mild transient tachypnoea, atelectasis and sometimes even respiratory failure [10, 62, 63]. This can be explained by the impaired clearance of amniotic fluid in the newborn lungs [8, 10, 64]. In the first days of life, these newborns already display a persistent rhinitis, nasal blockage or obstruction, which often leads to feeding difficulties. CRS usually develops during school age and lasts through adulthood. In PCD, CRS is often accompanied by nasal polyps [65]. Daily wet cough and chronic otitis media with consecutive conductive hearing loss due to middle ear effusion are also frequent symptoms from early childhood [11, 47, 65]. Drainage of the middle ear by inserting grommets commonly leads to chronic purulent otorrhoea and should be indicated very cautiously [9, 11, 66, 67].

Lower respiratory tract symptoms include recurrent bronchitis and pneumonia, which often begin in infancy. Chronic infection is prevalent in all individuals from school age. Infection and inflammation lead to mucus hypersecretion, lung consolidations, atelectasis and bronchiectasis [10, 68, 69]. Typically, the middle lobe and the lingula are affected initially, followed by the lower lobes. The upper lobes are involved at an advanced disease stage [68], in contrast to CF, where bronchiectasis usually involves the upper lobes at a young age [69]. As PCD does not affect the hepatobiliary and pancreatic functions, individuals with PCD, unlike CF patients, usually do not suffer from nutritional, liver or diabetic problems [9, 11].

Fundamental data on epidemiology, clinical presentation, course and treatment strategies are lacking in PCD, but are now collected in a recently developed international PCD registry [70]. Preliminary data suggest that life expectancy is more favourable than in CF [10, 71].

Diagnostic approaches

CRS is a clinical diagnosis made if ARS symptoms are present for $\geqslant$12 weeks. Current guidance for the diagnosis of CRS is given by the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS2012 [1]). The clinical definition of rhinosinusitis includes nasal blockage, obstruction or congestion, or nasal discharge (anterior/posterior nasal drip) and one of the following symptoms: facial pain or pressure, or reduction or loss of smell [1]. In addition, either endoscopy to identify nasal polyps and/or mucopurulent discharge and/or oedema or mucosal obstruction, or CT to identify mucosal changes must be performed [1].

Non-CF bronchiectasis

The diagnosis of bronchiectasis is usually made by HRCT [4]. Bronchiectasis can be classified as diffuse or focal and as cylindrical, varicose or saccular. Focal bronchiectasis can be secondary due to anatomical abnormalities of the bronchial or vascular system, foreign body aspiration, airway tumours, severe pneumonia or congenital parenchymal malformations. Diffuse bronchiectasis is often associated with multisystemic diseases [72], such as CF, PCD [10], immunodeficiencies [73], α_1-antitrypsin deficiency [74], rheumatoid arthritis and inflammatory bowel disease. However, even after thorough evaluation, the underlying cause of bronchiectasis remains unclear in 50% of cases [4, 57].

Conventional radiographs have a low sensitivity for the diagnosis of bronchiectasis and are suitable only for follow-up investigations of individual patients to monitor the disease course [58]. Patients with non-CF bronchiectasis should be assessed regularly in order to monitor the course of the disease and to identify complications, such as infectious exacerbations. During these visits, a microbiological work-up of sputum and nasal lavage samples is recommended [75]. Sputum samples often grow *Haemophilus influenzae*, followed by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa* and *Aspergillus* spp. [58, 75]. As in patients with CF, *P. aeruginosa* is associated with a more severe lung disease leading to worsening of the prognosis [60, 76–78]. If an *Aspergillus* sp. is present, an allergic bronchopulmonary aspergillosis should be considered [76]. In addition, lung function analyses are necessary.

Primary ciliary dyskinesia

PCD is both underdiagnosed and diagnosed too late [29]. Therefore, clinicians should initiate a diagnostic work-up in patients with typical phenotypes (table 1). Establishing a

PCD diagnosis is complex because of the high genetic and phenotypic variability. Currently, mutations in 35 genes have been identified as being causative for PCD (table 2) and the number of new genes is growing rapidly. Even when using advanced sequencing techniques, only ∼70% of PCD cases can be identified by genetic testing. Therefore, diagnosing PCD requires a combined approach of complementary tests (table 3).

Therapeutic approach

EPOS2012 defines a current standard of a therapeutic approach for CRS with and without nasal polyps (CRSwNP and CRSsNP, respectively) [1]. Therapy is focused on alleviating symptoms and controlling local disease. Conservative therapy mainly includes nasal application of corticosteroids and nasal (saline) irrigation. As a general rule, patients with severe CRSwNP should be considered to receive topical intranasal corticosteroids. It has been shown that this treatment is effective in reducing the size of nasal polyps, the symptoms of nasal obstruction, secretion and sneezing [20]. There is no evidence for the use of systemic corticosteroids in CRSsNP patients. Long-term antibiotic treatment (>12 weeks) with macrolides is recommended for patients with CRS (both CRSwNP and CRSsNP) who do not respond to corticosteroids and nasal irrigation [1, 124, 125]. Functional endoscopic sinus surgery should be performed if conservative treatment approaches are not successful. Surgery should be combined with appropriate medical therapy pre- and post-operatively [126].

Management of patients with non-CF bronchiectasis involves a multimodal therapeutic approach including airway clearance, reduction of airway infection, inflammation and tissue damage, and prevention and treatment of exacerbations. Guidelines suggest that patients with non-CF bronchiectasis should be instructed in airway clearance techniques and should routinely perform exercises [39, 41].

Long-term oral antibiotic treatment with macrolides seems to be effective, but it remains unclear which patients benefit from this treatment [39]. In clinical practice, patients with three or more exacerbations per year, with colonisation of *P. aeruginosa* or with impaired QoL under standard therapy are treated. In addition to their antimicrobial effect, macrolides show an anti-inflammatory effect [127]. However, further research is needed to

Table 1. Recommendations for candidates to be considered for PCD testing

1) Individuals with situs inversus totalis, other situs abnormalities or congenital cardiac defects (particularly if they have typical symptoms (see point 2))
2) Individuals presenting upper and lower airways disease independent of situs abnormalities:
    - Upper respiratory tract: persistent rhinitis or nasal discharge, chronic sinusitis, and chronic middle ear infection with or without hearing impairment
    - Lower respiratory tract: persistent wet cough, atelectasis or bronchiectasis (especially in the middle lobe, lingula or lower lobes, respectively), chronic/recurrent bronchitis and/or pneumonia
3) Unexplained neonatal respiratory distress syndrome with upper and lower respiratory symptoms and/or neonatal intensive care admittance
4) Siblings of PCD individuals, particularly if they have typical symptoms (see point 2)

Information from [8, 28].

Table 2. Genes associated with PCD[#] and corresponding ultrastructure

Gene [ref.]	**Axonemal/cellular component or function**
DNAH5 **[79–81];** ***DNAI1*** **[82–84];** ***DNAI2*** **[85, 86];** ***DNAL1*** **[87];** ***NME8*** **(*TXNDC3*) [88]**	Outer dynein arm subunit
CCDC114 **[89, 90];** ***ARMC4*** **[91];** ***CCDC151*** **[92];** ***TTC25*** **[93]**	Outer dynein arm targeting/docking factor
DNAAF1 **(*LRRC50*) [94];** ***DNAAF2*** **(*KTU*) [95];** ***DNAAF3*** **[96];** ***HEATR2*** **[97];** ***LRRC6*** **[98, 99];** ***ZMYND10*** **[99];** ***DYX1C1*** **(*DNAAF4*) [100];** ***SPAG1*** **[101];** ***CCDC103*** **[102];** ***C21ORF59*** **[103];** ***PIH1D3*** **[104]**	Cytoplasmic dynein arm assembly or transport factor
RSPH1 **[105, 106];** ***RSPH3*** **[107];** ***RSPH4A*** **[108];** ***RSPH9*** **[108]**	Radial spoke head homologue subunit
CCDC39 **[109];** ***CCDC40*** **[110]**	Nexin link/dynein regulator complex
CCDC164 **[111];** ***CCDC65*** **[103, 112];** ***GAS8*** **[113, 114]**	Nexin link subunit
DNAH11 **[115–118]**	Outer dynein arm subunit
HYDIN **[119]**	Central pair subunit
CCNO **[120];** ***MCIDAS*** **[53]**	*CCNO*: cytoplasmic centriole assembly and docking factor; *MCIDAS*: nuclear regulator of *CCNO* and *FOXJ1*
OFD1 **[121];** ***RPGR*** **[122]**	Role in motile cilia unknown; functions related to nonmotile cilia

[#]: currently, only ~70% of PCD cases can be identified by genetic testing.

clarify the exact therapeutic indication for long-term antibiotics [128]. In CF patients, therapy with inhaled antibiotics leads to a reduction of bacterial density, infective exacerbations and airways inflammation [129]. For patients with non-CF bronchiectasis, there are limited data available and further research is needed.

Surgical therapy, such as lobectomy, bears the risk of removing healthy lung tissue. Therefore, lung surgery should only be considered if the symptoms of a patient under best medical treatment cannot be controlled [39].

The therapeutic goal of PCD treatment is a reduction of disease progression and prevention of exacerbations and complications. As PCD is a rare disease, evidence-based data on therapeutic management are currently not available [130]. Most treatment regimens are deduced from studies in CF or other respiratory diseases. It is believed that PCD patients benefit from regular follow-up visits in specialised centres [66]. During these visits, microbiological testing of sputum and nasal lavage, lung function analyses, and assessment of upper and lower airway clearance techniques should be performed. Further regular assessments include hearing tests and diagnostic imaging [47, 131].

General recommendations include the avoidance of harmful agents such as cigarette smoke [8]. Airway clearance techniques should be performed routinely to aid mobilisation and expectoration of sputum [66]. In the case of infective exacerbations, antibiotic treatment should be performed based on the antibiogram of previous sputum samples. Harmful pathogens such as *P. aeruginosa* should be eradicated promptly. However, there are no randomised trials supporting this recommendation, which is deduced mainly from CF

Table 3. Diagnostic tests used for establishing a PCD diagnosis

Method	Benefit	Limitation
Nasal nitric oxide level	Very low values in PCD; noninvasive; quick result; high sensitivity [123]	Decreased levels in other disorders, *e.g.* acute sinusitis or CF; rarely, normal values occur in some PCD cases
High-speed video-microscopy analysis	Direct analysis of ciliary beat pattern and frequency; different beating phenotypes can be distinguished [44]	Variants with a subtle beating abnormality may be interpreted as normal; secondary ciliary dyskinesia due to infection and inflammation is very common – distinction from PCD phenotype may be difficult
Transmission electron microscopy	Analysis of ciliary ultrastructure [28]	No ultrastructural abnormalities in ~30% of PCD cases; some variants with false-positive diagnoses (notably inner dynein arm defects)
Immunofluorescence microscopy	Analysis of protein components of the ciliary axoneme	No abnormalities in ~20% of PCD cases; technical difficulties if specimen contains a lot of mucus
Genetic testing	Direct identification of the underlying defect; feasible when using high-throughput technologies	Expensive; currently only ~70% of PCD cases can be identified by genetic testing; rare variants difficult to detect; significance of missense variants often uncertain

Information from [8].

guidelines. Based on experiences in CF, nebulised antibiotics or long-term antibiotics may be considered in patients with chronic infection or recurrent exacerbations.

CRS with persistent nasal blockage and discharge is treated by nasal irrigation and possibly by sino-nasal inhalation with hypertonic saline [8]. As PCD airways are always colonised with bacteria and infectious exacerbations are very common, topical steroids might increase the susceptibility to infections in PCD subjects. Therefore, topical steroids should be used cautiously because they might increase the risk of infections. Surgical therapy of nasal polyps in PCD should be performed only in cases of severe worsening of the nasal blockage. In some cases, surgery might improve CRS-related symptoms in PCD patients, with benefits in lung function, reduced lung infections and improved QoL [132].

Conclusions

Non-CF bronchiectasis and PCD are chronic mucopurulent lung disorders that are often (non-CF bronchiectasis) or always (PCD) associated with CRS. Individuals with non-CF bronchiectasis and CRS suffer from more severe lung disease than individuals with non-CF bronchiectasis alone.

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In PCD patients, CRS develops during school age and is a hallmark symptom prevalent in all PCD adults. PCD individuals often have CRS accompanied by nasal polyps. Diagnosing PCD requires a combined approach of different diagnostic tests. Therefore, the number of undetected cases is still high. CRS management in PCD and non-CF bronchiectasis is focused mainly on conservative management. Surgery should be performed cautiously due to a high tendency of recurrence of nasal polyps, mainly in PCD patients, but could improve CRS-related symptoms in a subgroup of patients.

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Air pollution and the nose in chronic respiratory disorders

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In vitro animal and human studies have assessed experimentally the effects of air pollution, demonstrating that it acts as an adjuvant for nasal allergic reaction and increases specific IgE levels. The mechanisms of the adverse effects of air pollutants include innate and adaptive immune responses, oxidative stress and gene–environment interactions. Although positive results have been obtained in small studies, large clinical trials are necessary to demonstrate the benefits of antioxidant and anti-inflammatory interventions, especially in subjects with specific genetic risks. Epidemiological surveys have shown that viral infection is a major triggering factor in asthma and, to a lesser extent, in COPD exacerbations. More generally, atopy seems to be a disease modifier in the relationship between air pollution and asthma. Indoor pollution such as moulds, mouldy odours, passive smoking and occupational exposure to high-molecular-mass agents (*e.g.* phthalates) are risk factors for rhinitis, as well as for asthma.

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Traffic-related air pollutants contain a mixture of particulate matter and atmospheric gases, such as ozone (O_3) and nitrogen dioxide (NO_2). Particles are usually designated PM_{10}, $PM_{2.5}$ and ultrafine, corresponding to particulate matter with diameters of <10, <2.5 and <1 µm, respectively. Diesel exhaust particles (DEPs), which generally belong in the $PM_{2.5}$ and ultrafine categories, are a major component of the particulate matter (*i.e.* up to 90% of the particulate matter derived from traffic sources) that contributes to outdoor air pollution in urban environments and are estimated to account for up to 80% of human exposure to airborne pollutants.

In this chapter, we describe the toxicology and mechanisms involved in the detrimental effects of air pollutants, and then discuss the epidemiological relationships between air pollutants and upper airways diseases in the context of chronic respiratory disorders.

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Toxicology

Although the exact mechanisms by which air pollution exerts its effects on the body remain to be fully defined, recent studies have highlighted the importance of oxidative stress, gene–environment interactions and epigenetic changes [1–4]. These studies have shown that gaseous and particulate air pollution act as an adjuvant on allergic reactions and increase specific IgE levels. Inflammatory effects are observed when the level of oxidative stress exceeds the natural antioxidant defence mechanisms. Genetic susceptibility and epigenetic differences among individuals are key intrinsic factors that determine individual responses. However, large clinical trials are still required to demonstrate the benefit of intervention studies, especially in subjects with specific genetic risks.

Diesel exhaust particles

Experimental work in human, animal and *in vitro* models has identified DEPs as potent immunological adjuvants that are capable of enhancing physiological responses to allergens.

In vitro *models*

DEPs can target a multitude of cell types, including resident cells, such as fibroblasts and epithelial cells, as well as immune regulatory cells, such as macrophages, mast cells, eosinophils, lymphocytes and dendritic cells. Exposure to DEPs can induce the generation of Th2 cytokines, chemokines and reactive oxygen species (ROS) by these cells. DEP-mediated expression of cytokines involves both the p38 and Akt signalling pathways, both of which converge on the NF-κB pathway [5]. DEPs can also induce IgE production by acting directly on B-cells [5–9]. Particulate matter may also perturb epithelial barrier function by disruption of intercellular tight junctions [10].

Animal models

Short-term exposure (~3 h) of guinea pigs to DEPs has been shown to augment their nasal hyperresponsiveness to histamine, as assessed by the frequency of sneezing and the amount of nasal secretion [11], while exposure for 5 weeks aggravated the nasal allergic reaction induced by repeated weekly nasal administration of ovalbumin [12]. In the latter study, the frequency of sneezing, severity of rhinorrhoea, number of epithelium and subepithelium nasal eosinophils, and blood anti-ovalbumin-specific IgE levels increased in a dose-dependent manner [12].

Repeated exposure of mice to intranasal DEPs in addition to intranasal ovalbumin has been shown to induce eosinophilic nasal inflammation [13] and an increase in specific anti-ovalbumin IgE [14].

In rats, DEPs have been shown to exacerbate allergic rhinitis. By promoting allergen delivery to subepithelial tissues, DEPs can exacerbate the immediate allergic response. This occurs by an ROS-mediated pathway that disrupts tight junctions, thereby leading to increased permeability of nasal epithelial cells [15].

Human models

DEPs exhibit both specific and nonspecific effects in nasal provocation studies. Among the nonspecific effects that have been documented, an intermediate dose of DEP (*i.e.* 0.3 mg, which is equivalent to ~40 h of ambient exposure in the Los Angeles metropolitan study area) applied directly to the nasal mucosa resulted in readily detectable levels of IL-2, IL-4, IL-5, IL-6, IL-10 and IL-13 mRNA 18 h after the nasal challenge [16]. In another study, nasal DEPs induced a significant rise in the level of epsilon mRNA and of total IgE proteins in nasal lavage fluids 4 days after nasal challenge [17]. DEPs also increased the expression of CC chemokines (*e.g.* RANTES (regulated on activation, normal T-cell expressed and secreted), macrophage inflammatory protein (MIP)-1α and human monocyte chemotactic protein (MCP)-3) and nasal cellular inflammation [18].

Among the specific effects that have been documented are the DEP adjuvant effects on allergic responses in atopic subjects. DEPs coadministered with allergens have been shown to induce a significant increase in nasal symptom scores within minutes, with a 3-fold rise in nasal histamine levels in dust mite-sensitive subjects [19]. It was also found that lower allergen doses were required to induce symptoms [1]. A combined intranasal challenge with DEPs plus ragweed allergen skewed cytokine production to a Th2 pattern, with elevated IL-4 and decreased IFN-γ levels, increased expression of CC chemokines (*e.g.* RANTES, MIP-1α and MCP-3) and nasal cellular inflammation within hours in allergic subjects [20]. Within days, it also induced a large increase in ragweed-specific IgE and IgE-secreting cells in the nasal mucosa [20, 21].

Lastly, pre-exposure to DEPs prior to repeated nasal immunisations (*e.g.* three doses at 2-week intervals) with the neoantigen keyhole limpet haemocyanin resulted in the production of anti-keyhole limpet haemocyanin IgE. This study hence demonstrated that repeated DEP exposure can act to induce a long-term allergic response to primary allergic sensitisation [22].

Together, these various experimental studies show that DEPs, when combined with allergens, are capable of increasing the number of inflammatory cells, such as neutrophils, macrophages and lymphocytes, as well as the levels of pro-inflammatory Th2 cytokines and specific IgEs, thus acting as an adjuvant to allergic reactions.

Atmospheric gases

Ozone

It is well established that inhalation of O_3 generally exacerbates nasal allergic responses to allergens in animals [23] and humans [24, 25], while acute pronounced exposure to O_3 causes epithelial injury that results in cell death and neutrophilic rhinitis in animals [26, 27] and humans [28]. By contrast, it has recently been shown that chronic O_3 exposure can be associated with persistent nasal epithelial alterations (in infant monkeys) [29] and with eosinophilic rhinitis (in mice) [30].

Nitrogen dioxide

The major source of anthropogenic emissions of NO_2 is outdoor road traffic emissions and indoor gas cookers. The World Health Organization (WHO) suggests an annual mean value of 40 $\mu g \cdot m^{-3}$ (~0.02 ppm) and a 1-h mean of 200 $\mu g \cdot m^{-3}$ (0.1 ppm), respectively [31].

In an *in vitro* study, nasal epithelial cells cultured from tissues obtained from patients with atopic rhinitis during the pollen season released significantly greater amounts of IL-8 and RANTES after exposure to 400 ppb NO_2 for 6 h compared with cells of nonatopic individuals [32]. In another *in vitro* study, nasal epithelial cells of nonallergic subjects reacted *via* an inflammatory response (an increase in IL-6 and IL-8) to the combination of NO_2 (0.1 or 1 ppm for 1 h) and the house dust mite allergen Der p 1 [33].

In asymptomatic grass seasonal allergic rhinitis volunteers, pre-exposure to NO_2 (400 ppb) for 6 h increased nasal influx and activation (increase in eosinophilic cationic protein) of eosinophils to local allergen challenge. This increase was inhibited by pre-treatment with fluticasone propionate for 4 weeks [34].

Vagagginini *et al.* [35] studied the effects of NO_2 for 1 h on the airways of mildly asthmatic subjects. In contrast to O_3, no modifications were seen in the nasal lavage and sputum differential counts.

In conclusion, NO_2 is probably less potent than O_3 as an oxidant pollutant, but may be an initial step in allergen sensitisation.

Mechanisms of adverse effects of air pollutants

Multiple mechanisms have been proposed with regard to the adverse physiological effects of air pollutants. Among these, immune responses, oxidative stress and gene–environment interactions have received the most attention.

Immune mechanisms

Protection of the host against exposure to air pollutants involves both the innate and adaptive immune systems.

Innate immune mechanisms

Endotoxins (or lipopolysaccharides) are major outer-membrane components of Gram-negative bacteria [36]. Importantly, they have been shown to be present in particulate matter, and account for a large part of the effects of particulate matter on human airway macrophages [37]. By causing the release of cytokines from epithelial cells that activate resident airway macrophages, Toll-like receptor 4 (TLR4), a receptor for lipopolysaccharide, plays a critical role in inflammatory responses induced by air pollution [38]. *In vitro*, DEPs accentuate responses to very small doses of TLR agonists, such as lipopolysaccharide [39]. Activation of innate immunity results in the release of cytokines such as IL-1, IL-6, tumour necrosis factor and granulocyte–macrophage colony-stimulating factor, as well as alteration of epithelial barrier function, with an increase in cell permeability and apoptosis. Pollutant-induced alterations in TLR recognition may contribute to the concomitant increased susceptibility to viral infections. Air pollutants also interfere with inflammasome activation and cleavage of the pro-forms of IL-1β, IL-18 and IL-33 into active forms [40].

Adaptive immune mechanisms

Dendritic cells are key players in the initiation of T-cell immunity. Conventional dendritic cells are central to inducing sensitisation. *In vitro* and *in vivo* data have demonstrated that DEP exposure promotes conventional dendritic cell maturation and induction of a Th2 polarisation, with production of cytokines IL-4, IL-13 and IL-10 [41–43].

Both animal and human studies have shown that particulate matter exposure enhances antigen-induced IgE and Th2 cytokine production [44, 45].

IL-17-mediated inflammation has been shown to be induced after exposure to air pollution. IL-17 is a cytokine generated by T-cells, and contributes to host defences against bacterial and viral infections. In a murine model, intranasal administration of atmospheric particulate matter was shown to alter T-cell function by enhancing Th17 polarisation through the aryl hydrocarbon receptor. This receptor is considered to be the main receptor for polycyclic aromatic hydrocarbons (PAHs), a major component of DEPs [46].

Treg cells play a key role in inhibiting IgE production in response to allergens [47], and this is controlled by Forkhead box transcription factor Foxp3 [48]. In an *ex vivo* study performed in healthy individuals, different PAHs were found to induce opposite effects on the transformation of Treg cells into effector T-cells as a result of epigenetic modifications of the *Foxp3* gene. Thus, phenanthrene (figure 1a) induced the transformation of Treg cells into Th2 cells, whereas tetrachlorodibenzodioxin (figure 1b) induced the transformation of Treg cells into Th17 cells [49]. Other mechanisms of action of DEPs include disruption of tight junctions of the nasal epithelial barrier, thereby promoting allergen delivery into adjacent subepithelial tissues [15].

Oxidative stress and antioxidant defence responses

Ultrafine DEPs consist of a carbon core, which may also contain transition metals and redox-active chemicals such as quinones and PAHs. These entities can generate ROS, thereby leading to activation of intracellular signalling pathways that in turn can cause oxidative stress. Experimental models suggest that DEP organic carbon moieties, especially PAHs and quinones, may constitute an important variable that can affect experimental protocols [13, 50]. *In vitro*, DEPs generate ROS in macrophages [51] and in bronchial epithelial cells [8, 52].

At low doses, oxidative stress has a protective effect *in vitro* by inducing the generation of antioxidant defence responses [9, 53]. This is thought to involve the transcription factor nuclear factor E2-related factor 2 (Nrf2) and enzymatic antioxidants (*e.g.* superoxide dismutase, catalase, haem oxygenase-1, glutathione peroxidase and phase II enzymes (conjugation), such as glutathione *S*-transferase (GST)), as well as nonenzymatic antioxidants, such as vitamins and glutathione. By ROS scavenging and metabolism of reactive chemicals, these antioxidant responses suppress the pro-inflammatory effects of air pollutants [54].

Inflammatory effects are observed when the level of oxidative stress exceeds the natural antioxidant defence mechanisms (figure 2). These inflammatory effects occur as a result of activation of the transcription factor NF-κB, with production of pro-allergic Th2 cytokines

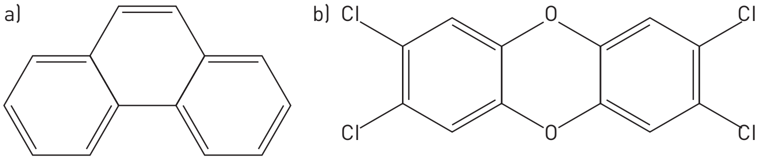

Figure 1. Two polycyclic aromatic hydrocarbons: a) phenanthrene and b) tetrachlorodibenzodioxin.

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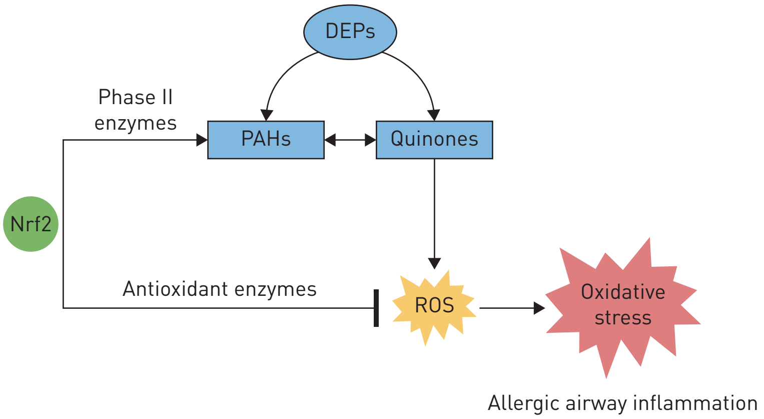

Figure 2. Diesel exhaust particles (DEPs) may contain polycyclic aromatic hydrocarbons (PAHs) and quinones, which can general reactive oxygen species (ROS) leading to oxidative stress. Nuclear factor E2-related factor 2 (Nrf2), induced by ROS, activates phase II and antioxidant enzymes, which decreases ROS.

and adhesion molecules contributing to the adjuvant effect of DEPs [55]. In a final stage, cytotoxic effects can also involve mitochondria, which are capable of inducing cell apoptosis.

Gene–environment interactions

The physiological responses to air pollution vary greatly. Genetic susceptibility and epigenetic differences between individuals are key intrinsic factors that determine individual responses (figure 3).

Genetic polymorphisms

Most of the studies to date have highlighted the importance of oxidative stress genes, such as GST and TLR genes. Hydroxyl radicals induce a decrease in glutathione, which in turn induces transcription of GST genes. The GST polymorphism gene product GSTM1 is involved mainly in detoxification of PAHs, while GSTP1 detoxifies lipid peroxidation products and DNA oxidation products. Individuals with a deficiency in the GST gene, such as antioxidant *GSTM1*-null alleles (*i.e.* *GSTM1* deletion polymorphisms, which occur in about 50% of normal individuals) and *GSTP1* Ile/Ile have lower expression levels of the corresponding antioxidant proteins [56].

Modulatory effects of antioxidant gene polymorphisms have been seen in allergic responses to ragweed with a particulate challenge. In these patients, a DEP nasal challenge exacerbated allergic responses after ragweed provocation, with a higher specific IgE response in *GSTM1*-null and *GSTP1* Ile/Ile genotypes [45].

PAHs have been shown to potentiate the *in vitro* chemokine (*e.g.* IL-8 and RANTES) response induced by the TLR3 ligand polyinosinic–polycytidylic acid.

Epigenetic mechanisms

An epigenetic trait is defined as a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence itself. The main mechanisms involved are DNA methylation, histone acetylation and expression of microRNAs (miRNAs).

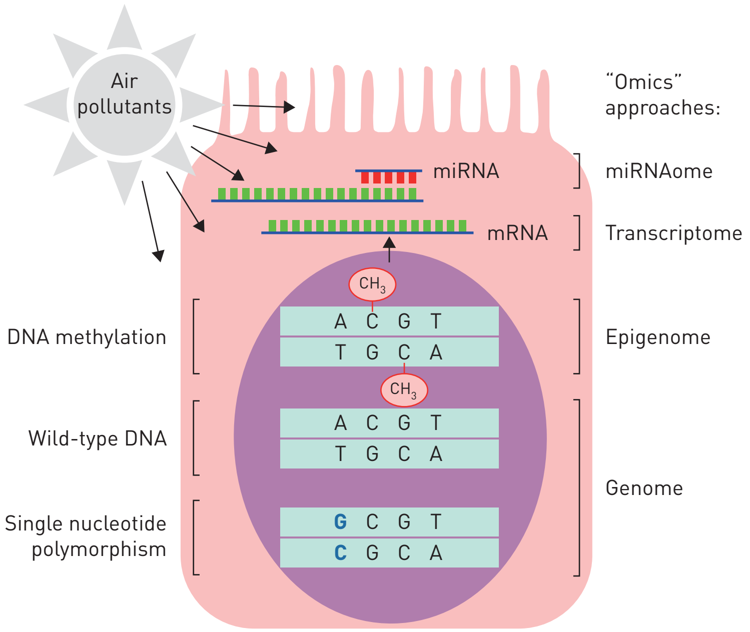

Figure 3. The response to air pollutant exposure in the nose may vary based on single nucleotide polymorphisms in the DNA comprising the genome, differences in DNA methylation and other epigenomic changes, and altered microRNA (miRNA) expression in the miRNAome. Reproduced and modified from [3] with permission from the publisher.

Changes in the DNA methylation of the IFN-γ and IL-4 promoters in mice have been observed after combined DEP and *Aspergillus fumigatus* nasal exposure, and these correlated with IgE production [57]. In healthy adults, controlled exposure to fine concentrated ambient particles for 2 h was shown to lower *Alu* methylation, while exposure to coarse particles lowered *TLR4* methylation [58]. In another crossover study, genes encoding protein kinases and other proteins involved in the NF-κB pathway became less methylated after exposure to DEPs for 2 h on two separate occasions that were 2 weeks apart [59].

Histone acetylation (a reversible phenomenon) leads to unwinding of the chromatin structure, thereby providing transcription factors with better access to promoter sites. Histone acetyltransferases promote acetylation, while histone deacetylases promote deacetylation. Nasal mucosal responses may differ from those in the lower airways, although whole-genome studies have shown that nasal epithelial responses to toxins are similar to bronchial epithelial responses [60]. In an *in vitro* model, epithelial IL-8 release by PM10 exposure was associated with increased acetylation of histone proteins. This was mediated by oxidative stress, as demonstrated by thiol antioxidant inhibition [61].

miRNAs are endogenous, single-stranded, short noncoding RNA entities that negatively or positively regulate expression of specific genes at the post-transcriptional level. Using both *in vitro* and human studies, miR-10b and miR-128 miRNAs have been identified as being associated with air pollution exposure [62].

Further studies should be conducted to ascertain the short- and long-term impacts of the timing, load and duration of air pollution on epigenetic expression, and to translate these findings into clinical applications.

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Interventions

In vitro and human studies have indicated that some antioxidant supplements can alleviate the inflammatory effects of air pollution. Thus, sulforaphane is capable of inducing an enzymatic antioxidant response after upregulation of Nrf2. This entity, which is found naturally in cruciferous vegetables, has been shown *in vitro* to reverse the disruption of epithelial barrier function induced by exposure to particulate matter [10]. In a human nasal provocation study, a sulforaphane-rich preparation from broccoli increased the expression of airway epithelial cell antioxidant enzymes in a dose-dependent manner [63] and attenuated the nasal allergic reaction to DEPs [64].

Daily supplements of vitamins C and E administered for 6 weeks were associated with stable levels of IL-6 in the nasal lavage of young asthmatic subjects after O_3 exposure, while there was a significant increase in IL-6 in the placebo group [65].

However, as meta-analyses performed in cohort studies are still negative as well as underpowered, large clinical trials will be required to demonstrate the benefit of antioxidant interventions, especially in subjects with specific genetic risks.

Summary

Experimental work both *in vivo* and *in vitro* has shown that air pollutants increase the risk of respiratory disease by triggering innate and acquired immunity, generating ROS and altering gene expression [58]. However, these effects have only been shown at very high levels of pollutants. The effects of low concentrations of pollutants and the long-term effects of exposure to pollutants need to be addressed through additional and more thorough studies.

Epidemiological relationships between air pollutants and respiratory disorders

Here, we will discuss the relationship of chemical and physical, but not biological, air pollution, occurring both outdoors and indoors, to upper airways diseases in the context of chronic airway diseases. Thus, we will ignore the acute effects of air pollution changes in otherwise healthy subjects. Because the literature is so dense, we will focus on recently published studies. This topic is less often discussed than that of chronic lower airways diseases, probably because the latter implies more severe morbidity and sometimes mortality, and also because assessment of the upper airways is more difficult than that of the lower airways.

Outdoor air pollution

Acute effects: asthmatic patients

Many epidemiological studies have demonstrated strong associations between air pollution and asthma exacerbation, but involvement of the upper airways is seldom acknowledged. In contrast, symptoms linked to viral infections are well-known triggering factors in asthma exacerbations. Using a mathematical model of viral transmission, Puranik *et al.* [66] concluded that, in children, daily viral prevalence is the strongest predictor of asthma exacerbation, and that transmission went down by 45% in children during the school holidays and increased again when school resumed (“back-to-school exacerbations”).

EGGO *et al.* [67] found that viral infection cause the majority of severe asthma exacerbation in children, particularly in atopic children.

In both asthma and COPD patients, heavy car traffic, influenza virus infection, cold temperatures and increased air pollutant concentrations are potential contributors to the burden of exacerbations in the community [68].

Chronic effects: asthma and allergy

Many studies have been published in this field. We will summarise them according to the structure of the study.

Retrospective studies use health data collected primarily for administrative purposes. These data, usually collected on a daily basis, are compared with daily air pollution levels provided by air monitoring stations. The advantage of such a design is that the information is readily available. Thus, such studies are quick to perform and cheap. Their drawback is the lack of data about possible confounding factors, which may obscure the relationship between exposure and disease. HAYAT *et al.* [69] performed a time-series survey in primary care relating the timing of general practitioner consultations for upper respiratory disease to the daily level of main pollutants, after adjustment for several potential confounders. The study included 295 740 outpatient visits from January 1992 to December 1994. The survey demonstrated a stronger association with PM10 changes than with sulfur dioxide and a stronger association in the elderly than in children. The effect, albeit relatively small on an individual basis, could be considerable on a community basis because of the many consultations in primary care. Using a similar format, CHEN *et al.* [70] analysed daily clinic visits for allergic rhinitis with respect to daily air pollution levels for the period 2006–2011, after controlling for weather variables, day of the week, seasonality and long-term trends. For most pollutants studied, there was an elevated risk of clinic visits on days with higher levels of air contaminants. It should be noted that these two studies did not evaluated chest symptoms.

In cross-sectional studies, data on health status and air pollution exposure are collected at the same time. As in retrospective studies, the advantage of such a study is the rapid gathering of data on exposure and disease, and thus it is relatively quick and cheap to undertake. Data on potential confounding factors can also be collected and included in the statistical analysis. Confounding bias, such as migration bias, may occur and should be kept in mind while designing the survey. Such a design was used by DEVAKUMAR *et al.* [71] in Nepal who used the ISAAC (International Study of Asthma and Allergies in Childhood) protocol in 834 children and failed to demonstrate an association between rhinitis symptoms and personal estimates for air pollution. They did not demonstrate an association between PM4 and symptoms of asthma and rhinitis, except for dry cough and wheeze in the last 12 months in boys. In fact, a WHO review of the evidence showed an association of air pollution with cough only [72].

DELL *et al.* [73] carried out a nested case–control survey performed in 1497 children aged 5–9 years living in Toronto, Canada, showing that their current and lifetime exposure to NO_2 were predictive of asthma, but only in children with a personal history of allergic disease. This characterised atopy as a disease modifier in the relationship between traffic-related air pollution and asthma. JUNG *et al.* [74] reported a cross-sectional survey performed in primary school children living in 10 Korean cities and using as a proxy of environmental exposure to air pollutants distance to the nearest main road, total road

Table 1. Cohort studies relating air pollution exposure to rhinitis and asthma

Setting [ref.]	Main outcome	Main result
2598 preschool children [78]	Allergic rhinitis	Prevalence of allergic rhinitis associated with pre- and post-natal exposure to air pollution; genetic predisposition acts as a modifier
PARIS (Pollution and Asthma Risk: an Infant Study) cohort study [79]	ENT and respiratory symptoms	A parental history of allergy, stressful family events and male sex increased susceptibility to air pollutants in children
Meta-analysis of four birth cohort studies [80]	Rhinitis and asthma	Risk of incident asthma increased in relation to NO_2 and $PM_{2.5}$; no relationship with rhinoconjunctivitis
Melbourne atopy cohort study [81]	Hay fever, wheezing and asthma at 12- or 18-year follow-up	No overall relationship although an association with wheezing and asthma in *GSTT1*-null carriers
PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study [82]	Asthma, hay fever allergic sensitisation, lung function and NO_2	Asthma incidence, prevalence of asthma and rhinitis symptoms associated with oxidative potential

NO_2: nitrogen dioxide; $PM_{2.5}$: particulate matter with diameter <2.5 µm; *GSTT1*: glutathione *S*-transferase T1 polymorphism gene.

length of main roads and proportion of the main road area within a 200 m home area. Exposure to traffic-related air pollution was associated with increased risk of asthma, allergic rhinitis and allergic sensitisation, and with reduced lung function. Using a similar design in South Africa, Shirinde *et al.* [75] demonstrated a higher prevalence of allergic rhinitis and rhinoconjunctivitis, but not hay fever, in children living in areas with heavy traffic-related air pollution, but this survey did not asked about asthma or asthmatic symptoms. Deng *et al.* [76] suggested that maternal exposure to the traffic-related air pollutant NO_2 during pregnancy was associated with eczema for the first trimester, asthma for the second and allergic rhinitis for the third. In Seoul, Korea, Seo *et al.* [77] used a geographically weighted regression model to evaluate the impact of PM_{10} on inpatient and outpatient count data for atopic dermatitis, asthma and allergic rhinitis. Thus, PM_{10} measurements at 25 monitoring stations in the city were interpolated to 424 subdistricts where data about allergic diseases were gathered. No significant effect of PM_{10} was observed on allergic rhinitis and asthma when potential confounding factors were controlled.

Cohort studies (table 1) are best for causal inference because the data are collected prospectively. When considering a limited group of subjects followed up during a limited time period, they are named "panel" studies. They allow the best inference for causation but are costly and time-consuming. A cohort study performed in 2598 Chinese children aged 3–6 years showed that the lifetime prevalence of allergic rhinitis was associated with pre- and post-natal exposure to traffic-related air pollution [78]. Sensitivity analysis demonstrated that genetic predisposition by parental atopy acted as a modifier. In the PARIS (Pollution and Asthma Risk: an Infant Study) cohort study, a parental history of allergy, stressful family events and male sex all increased susceptibility to adverse respiratory effect, such as persistent wheezing, dry cough and rhinitis symptoms [79].

GEHRING *et al.* [80] performed a meta-analysis including four birth cohort studies of 14 126 children followed up for 14–16 years. The risk of incident asthma was increased with NO_2 exposure and PM2.5 absorbance. In contrast, no relationship to rhinoconjunctivitis was demonstrated. Polymorphisms in genes involved in the oxidative stress response may in part account for the heterogeneous associations between traffic-related air pollutants and health impact, notably asthma and allergy [81, 82].

In summary, the majority of these surveys showed a relationship between long-term exposure to traffic-related air pollution and rhinitis, asthmatic symptoms and diagnosis of asthma. However, is it *de novo* asthma or pre-existing asthma revealed by exposure to air pollution, especially in children with low anti-oxidative potential? In addition, the relative risk demonstrated in cohort studies is very low at an individual level. The fact that risk is very low could also be accounted for by inaccuracy in evaluating personal exposure to air pollutants, because indoor air pollution has not been directly measured, even if it is taken into account by inclusion of passive smoking and housing conditions in the model. Identification of health outcome through standardised questionnaires can also be questioned.

Intervention

Avoidance of outdoor air pollution is hard to achieve because there is no realistic way of avoiding exposure. National authorities do not recommend that asthmatic subjects remain indoors during periods of elevated air pollution because indoor air pollution can in fact be more harmful. When the air quality index reaches a certain level, asthmatic patients, and eventually all individuals, should reduce the time spent outdoors, and in particular avoid exertion in the polluted air [83]. Other recommendations, such as wearing a dust mask and taking supplemental antioxidants, are unlikely to be effective [84]. Thus, sustained clean air policies remain the most effective way to reduce health effects that are related to air pollution.

In this respect, a study was performed in a group of asthmatic children living in the London Low Emission Zone. Data on air pollution were gathered before and following its implementation. Information on respiratory and allergic symptoms was obtained through parent-completed questionnaires. It was found that the London Low Emission Zone did not reduced ambient air pollution levels or symptoms over the study period [85]. By contrast, in California, decreased levels of particulate and gaseous air pollutants (apart from O_3) have been obtained over the last decade. In parallel, the pulmonary function of adolescents has improved over time, but no data on ENT symptoms were available [86].

Indoor air pollution

We will present some new studies performed in homes, but also in schools, long-term care residences for the elderly and in the occupational context, illustrating some possible new air contaminants.

In China, LIN *et al.* [87] evaluated the impact of the first 2-year home environment on new-onset and remission of asthma and allergic symptoms in 4246 preschool children. Visible mould, mouldy odour, air dryness, stuffy odour and parental smoking were consistently positively associated with the new onset of symptoms. Over half of the families had brought new furniture or decorations during this time period, but there was no relationship to symptom occurrence. In Japan, AIT BAMAI *et al.* [88] measured several phthalates in 156 single-family homes and concluded that, although the associations were not statistically significant, levels of several phthalates were associated with the prevalence of allergic rhinitis, conjunctivitis and atopic dermatitis in children. In schools in four other European countries, SIMONI *et al.* [89] studied the respiratory health of 654 primary school children in relation to total viable moulds and fungal DNA, and concluded that children exposed to viable moulds at concentrations of >300 $\mathrm{CFU{\cdot}m^{-3}}$ had a higher prevalence of dry cough at night, persistent cough and rhinitis.

Conclusions

Experimental work both *in vivo* and *in vitro* has shown that air pollutants increase the risk of respiratory disease. They trigger innate and acquired immunity, generate ROS and alter gene expression [58]. However, these effects have only been shown at high levels of pollutants. The effects of low concentrations of pollutants and the long-term effects of exposure to pollutants warrant being addressed through additional and more thorough studies. These low levels are those encountered in epidemiological surveys, which undoubtedly demonstrate a worsening of symptoms during air pollution episodes and possibly the new occurrence of upper airways diseases following long-term exposure, especially in atopic individuals.

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Treating the nose for controlling the lung: a vanishing story?

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Despite historical studies showing the high prevalence of rhinitis and rhinosinusitis in asthma and COPD, and the impact of diagnostic and therapeutic neglect of rhinitis and rhinosinusitis on bronchial symptoms in these patients, routine clinical experience shows that a significant portion of asthma and COPD patients are deprived of proper care for upper airways disease. Rhinitis is considered a major risk factor for asthma, with growing evidence that timely treatment for allergic rhinitis might prevent the development of asthma. In addition, early-stage treatment for CRS has been shown to be associated with a lower prevalence of asthma. Undoubtedly, a significant portion of patients with asthma and COPD benefit from optimal medical and/or surgical treatment of the upper airways. The future challenge will be to predict who might benefit from referral to an ENT specialist to optimise the upper airways treatment, taking into account preventative, predictive and personalised care in the approach.

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The upper and lower airways are linked by epidemiological, physiological and pathological characteristics. This link has been studied repeatedly in the past, but it is only relatively recently that the concept of “united airways disease” has appeared in the official documents and guidelines of scientific societies [1, 2]. As the nose stands at the entry of the airway, it is not difficult to imagine that lower airways pathology may be triggered by nasal conditions causing obstruction [3]. Upper airways inflammation can be roughly divided into two clinical entities, *i.e.* rhinitis and rhinosinusitis, and the interaction between chronic upper and lower airways inflammation has been studied primarily in allergy (figure 1).

Rhinitis is defined as a symptomatic inflammation of the nasal mucosa, giving rise to specific symptoms [4], and its major phenotypes include allergic rhinitis, infectious rhinitis and nonallergic, noninfectious rhinitis [7]. Epidemiologically, rhinitis coexists in up to 90% of allergic asthma patients and in up to 80% of those with nonallergic asthma. Additionally,

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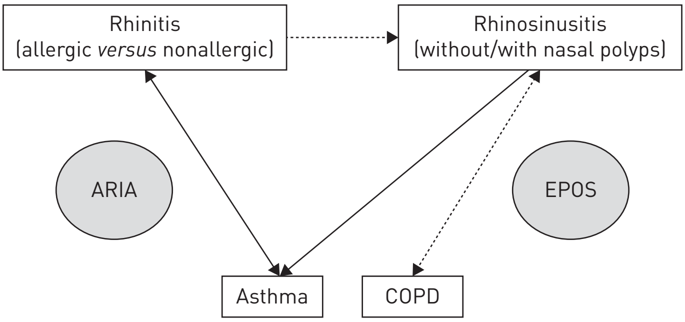

Figure 1. Interaction between different respiratory diseases. ARIA: Allergic Rhinitis and its Impact on Asthma [4]; EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps [5]. Reproduced and modified from [6] with permission from the publisher.

10–40% of allergic rhinitis patients suffer from asthma [8–14]. Rhinitis is a well-established risk factor for asthma development and persistence in both adulthood and childhood [15–17]. Interestingly, allergic rhinitis has been found to increase the risk of asthma arising later in life, independent of patient atopic status, while uncontrolled disease for a long time period is also linked with widening of the spectrum of allergy polysensitisation [8, 17].

Upper respiratory tract infections are also known to cause exacerbations of lower airways diseases, such as asthma and COPD. Human rhinovirus (hRV) is the most frequently detected pathogen, responsible for multiple wheezing episodes in the majority of school-aged children and in almost half of asthma exacerbation cases in adulthood [18, 19]. Among nonallergic, noninfectious rhinitis patients, occupational asthma and rhinitis appeared to coexist in up to 90% of patients in one study [20].

As discussed in detail in the most recent European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2012) [5] and Allergic Rhinitis and its Impact on Asthma (ARIA) publication [4], and in other chapters of this *ERS Monograph* [21], sino-nasal inflammation often coexists with lower airways diseases, such as asthma, COPD, CF, AERD and PCD. A large multicentre European epidemiological survey (the GA^{2}LEN (Global Allergy and Asthma European Network) survey) confirmed a strong association between CRS and late-onset asthma using symptoms proposed by the previous European Position Paper on Rhinosinusitis and Nasal Polyps (E^{3}POS [22]) to define nasal disorder rather than reported diagnosis [23]. Ponikau *et al.* [24] reported 91% of CRS patients having either asthma or increased bronchial hyperreactivity. Moreover, several research centres demonstrated the coexistence of CRS and clinical asthma in 50% of patients [25]. Additionally, sino-nasal symptoms are frequently mentioned by asthmatic patients, ranging up to 80% [5]. In parallel, sinus mucosal thickening has been documented in up to 84% of patients with severe asthma [26]. Interestingly, CRS with nasal polyps (CRSwNP) has been estimated to be present in 7% of asthmatic patients [27], and even more frequently in nonatopic and late-onset asthma patients (10–15%) [5, 27, 28]. Samter's Triad (also known as aspirin intolerance, AERD or NSAID-exacerbated respiratory disease), characterised by rhinosinusitis with polyposis, asthma and NSAID intolerance, is a distinct clinical entity with a prevalence of 1% in the general population and 10% among asthmatic subjects [29].

Despite clear evidence showing a causal relationship between upper airways pathology (rhinitis and rhinosinusitis) and lower airways pathology (asthma and COPD), no routine examination is performed to evaluate upper airways symptoms in patients with asthma and *vice versa*. Hence, a significant proportion of patients with asthma or COPD may benefit from routine clinical examination of the upper airways to better control their disease. The future challenge will be to predict who might benefit from a referral to an ENT specialist to optimise upper airways treatment, taking into account preventative, predictive and personalised care in the approach.

Impact of optimal nasal function on bronchial homeostasis

The nose and the bronchi are often studied as separate organs, despite the fact that they are anatomically connected, are both lined with a pseudo-stratified columnar epithelium, and are both equipped with innate and adaptive immune defence mechanisms. More importantly, both airway systems share the same important function, *i.e.* passage of air in and out of the lungs. Humidification, heating and filtration of inhaled air are the main functions of the nasal airways, whereas gas exchange takes place in the lungs (figure 2). Hence, optimal nasal function is mandatory for ideal pulmonary gas exchange. Hampered purification, humidification and/or warming of the inhaled air by the nose may therefore contribute to or induce bronchial pathologies in susceptible individuals. Indeed, >50% of patients with CRS have either asthma or bronchial hyperreactivity when challenged with methacholine [24, 25]. Alternatively, sino-nasal symptoms are reported in a certain percentage of asthmatic patients [22, 26]. Asthma and CRS share common histopathological and pathophysiological features, such as eosinophilic airway inflammation and epithelial remodelling, *e.g.* epithelial shedding and/or basal membrane thickening [24]. Cytokine patterns in the sinus tissue of patients with CRS provide an elegant representation of cytokine patterns in the bronchial tissue of asthmatic patients, explaining the presence of eosinophils in both conditions [31]. Eosinophils are the predominant cell type in both nasal and bronchoalveolar lavages in patients with CRS and asthma [32]. Interestingly, sinusitis and bronchial asthma have been

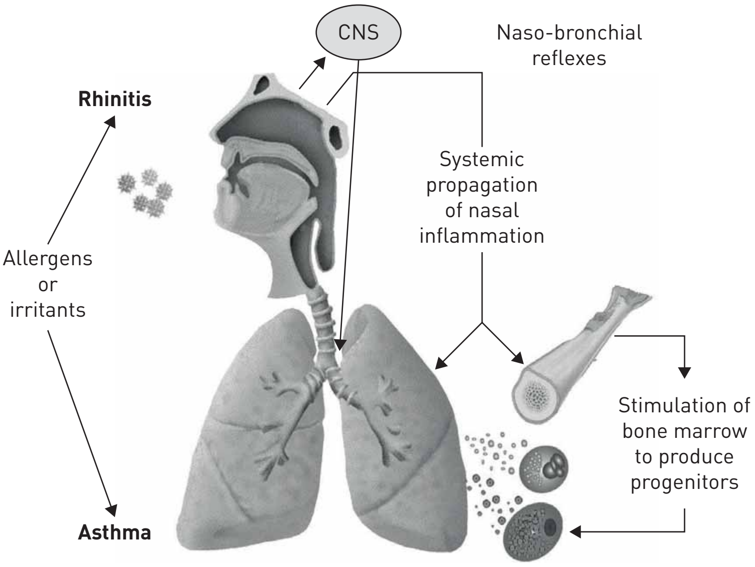
CNS
Naso-bronchial reflexes
Rhinitis
Systemic propagation of nasal inflammation
Allergens or irritants
Stimulation of bone marrow to produce progenitors
Asthma

Figure 2. Mechanisms explaining upper and lower airways interactions: the nose and bronchi are linked *via* direct, systemic and neural pathways. CNS: central nervous system. Reproduced and modified from [30] with permission under CC BY 4.0.

aetiologically linked to each other. Both diseases can affect and/or amplify each other *via* the systemic route and the bone marrow, and similar pro-inflammatory markers were found in the blood in experimental studies [33].

In CRSwNP, the underlying aetiology and mechanisms are more diverse, and different inflammatory patterns have been described. While CRSwNP is mainly considered a Th2-driven inflammation with expression of IL-5 and tissue eosinophilia, primarily neutrophilic types do also occur, predominantly in Asian subjects and in some populations in North America [34, 35]. Th2 inflammation with expression of IL-5 is associated with an increased risk of developing asthma. In recent years, new light has been shed on the pathology of CRSwNP, showing increased colonisation by *Staphylococcus aureus* and the presence of specific IgE against *S. aureus* enterotoxins (SE-IgE) in polyp tissue [36]. Notably, in subjects with CRSwNP and comorbid asthma or aspirin sensitivity, an increased rate of colonisation and IgE presence was noted in polyps. Hellings *et al.* [37] demonstrated that nasal application of *S. aureus* enterotoxin B in an experimental asthma mouse model is capable of aggravating asthma symptoms. More recently, Tomassen *et al.* [38], in a pan-European study, showed that the concentration of SE-IgE is associated with an increased risk of asthma. Bachert *et al.* [39, 40] demonstrated that an eosinophilic IL-5-positive endotype carries a risk of asthma of up to 70%. SE-IgE antibodies were significantly associated with asthma severity, oral corticosteroid use, lung function parameters and hospitalisations within the last 12 months. Sinusitis and asthma can aggravate each other *via* IL-5. Nasal application of *S. aureus* enterotoxin B induced release of IL-5, IL-4 and IL-13 in the lungs of mice [41]. In patients with CRSwNP, complete blockage of the nasal cavity will hamper the protective function of the upper airways, bypassing the nasal defence mechanisms and making the lower airways more vulnerable. This topic is discussed in more detail in the context of the mechanistic paradigm of asthma and nasal polyposis by Bachert *et al.* [42] elsewhere in this *ERS Monograph*.

The link between (optimal) nasal function and bronchial homeostasis has been studied extensively for allergic rhinitis and asthma. The concept of "united airways" allergy was included in the 2001 World Health Organization state-of-the-art ARIA publication [1]. Up to 90% of patients with asthma have allergic rhinitis and ~30% of allergic rhinitis patients suffer from asthma. Even so, the risk of developing asthma in a later phase is three times higher when a patient suffers from allergic rhinitis, irrespective of the atopic status [17].

In view of the interaction between the nose and the bronchi, treating the upper airways *via* medical and/or surgical approaches is important to stop the progression towards bronchial diseases (figure 3).

Impact of controlling nasal inflammation on the bronchi

Evidence-based guidelines for allergic rhinitis treatment are summarised in the ARIA documents [1, 4, 43, 44]. In view of the interaction between the upper and lower airways, it has been suggested that management of allergic rhinitis results in the alleviation of asthmatic symptoms. Reducing asthma symptoms by treating rhinitis can potentially decrease asthma-related healthcare resource utilisation and the associated costs, taking into consideration that allergic rhinitis tends to be undertreated in asthma patients [45]. Adequate treatment of allergic rhinitis in asthmatic subjects has been shown to improve asthma symptoms [46–48] and pulmonary function tests [47], and to reduce direct and indirect costs [49]. The risk of

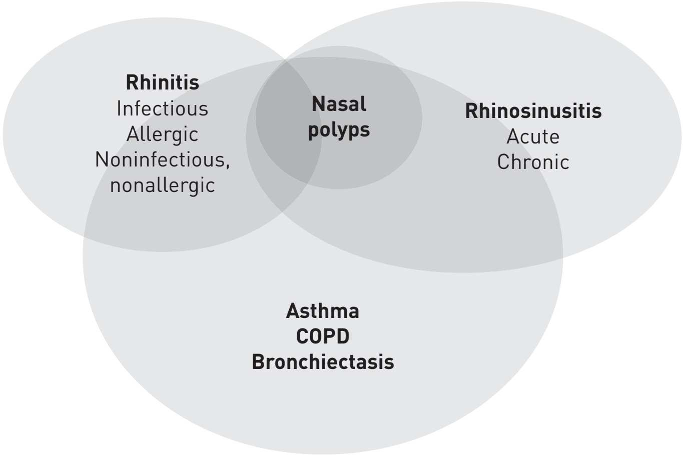

Figure 3. Scheme representing the close relationships between upper (rhinitis and rhinosinusitis) and lower (asthma, COPD and bronchiectasis) airways diseases. Reproduced and modified from [6] with permission from the publisher.

emergency room treatment or hospitalisations [50], exercise-induced asthma [51] and bronchial hyperresponsiveness [52, 53] was reduced, as well as the number of asthma-related hospitalisations and emergency department visits [54–56].

The efficacy of allergic rhinitis treatment in alleviating lower airways symptoms is best documented for nasal corticosteroids. Nasal steroids have been shown to reduce bronchial hyperresponsiveness in allergic rhinitis patients with or without clinical asthma [46, 52, 57]. One study reported that nasal corticosteroids are more efficient than inhaled steroids to control asthma symptoms [53]. Nasal steroids have been found to reduce asthma symptoms in patients with concomitant rhinitis [58] and to decrease asthma-related emergency department visits [56]. Recently, a randomised placebo-controlled trial in allergic rhinitis and intermittent asthma patients with mometasone furoate nasal spray demonstrated a significant improvement of the upper and lower airways and the global symptom score [59]. Overall, in patients with perennial rhinitis and intermittent asthma, mometasone furoate improved the QoL and the burden of respiratory symptoms. CRYSTAL-PETERS *et al.* [54] showed in a retrospective cohort of children and adult patients aged 12–60 years that treatment with intranasal corticosteroids decreased asthma-related events, such as hospitalisations, compared with untreated patients. In agreement with this, FUHLBRIGGE *et al.* [56] concluded that treatment with nasal corticosteroids for allergic rhinitis and possibly oral antihistamines was associated with a reduced risk of subsequent asthma-related events by >30% compared with patients who did not receive any treatment. In contrast, a recent large randomised placebo-controlled study did not report a beneficial effect of the use of nasal corticosteroids on asthmatic symptoms and bronchial responsiveness in patients with allergic rhinitis and concomitant asthma [60]. However, the authors concluded that a combination of intranasal and inhaled steroids is needed to control the seasonal increase in nasal and asthmatic symptoms of patients with pollen-induced rhinitis and asthma.

Oral or intranasal use of H_1-antihistamines has been proven to be very effective in the treatment of allergic rhinitis [4]. However, the effectiveness of antihistamines in improving subjective and objective asthma parameters in patients with allergic rhinitis has not been demonstrated consistently. Although not effective as a monotherapy for asthma, second-generation antihistamines might provide some protection against histamine-induced bronchoconstriction and are beneficial in patients suffering from allergic rhinitis and concomitant asthma [61, 62]. Cetirizine at up to twice the conventional dose improved symptoms and pulmonary function in some patients with mild seasonal or mild to moderate perennial asthma [63–65], although it has not been given to patients with severe asthma. Loratadine, at the conventional or twice the conventional dose, showed a trend towards improvement in patients with moderate asthma, but no appreciable effect in patients with more severe asthma. When combined with pseudoephedrine [66] or montelukast [67], loratadine reduced symptoms and rescue medication, and improved pulmonary function in patients with mild seasonal asthma. In a multicentre double-blind study, desloratadine treatment (5 mg once daily) *versus* placebo in 331 subjects with seasonal allergic rhinitis and mild seasonal allergic asthma resulted in significant relief from the signs and symptoms of seasonal allergic rhinitis [68]. Additionally, in this patient population, symptoms of seasonal allergic asthma also improved.

Cysteinyl leukotrienes are mediators of the pathogenesis of upper and lower airways allergy. Leukotriene receptor antagonists, besides alleviating the symptoms of allergic rhinitis and asthma, can also reduce the need for medication use for both pathologies [69–71]. Their effectiveness on global airway allergy treatment is justified, as cysteinyl leukotrienes promote eosinophil recruitment towards the airway and bone marrow eosinopoiesis upon allergen contact, making them an ideal target [72].

Allergen-specific immunotherapy (AIT) is another pillar of systemic therapy for allergic rhinitis patients. Besides a long-term reduction in allergic rhinitis symptoms and medication use [73], AIT is also reported to be effective in mild asthma and to prevent its development in allergic patients [74]. The protective effects of AIT, either subcutaneous or sublingual, on allergic diseases have been supported by ARIA guidelines [4]. Data provided by several published trials indicate that AIT is not only an effective treatment for allergic rhinitis but can also reduce asthma severity [74–77]. AIT can also prevent new sensitisations and halt the overall progression of asthma in children and adults with allergic rhinitis [74–77]. However, there is no consensus on which is the most relevant study design to assess AIT efficacy in asthma, and recently its preventative effect on asthma development has been questioned [78]. Younger age groups and polysensitised patients with a more severe allergic rhinitis phenotype are more likely to develop severe asthma and may therefore benefit from AIT [79–81].

Novel therapeutic approaches such as anti-IgE (omalizumab) treatment are under investigation for treating patients with upper and lower airways allergy [82]. The SOLAR (Study of Omalizumab in comorbid Asthma and Rhinitis) study [83] showed a significant improvement in asthma and rhinitis clinical symptoms, lung function parameters, and asthma- and rhinitis-related QoL in patients with concomitant pathology. In addition, patients under treatment with omalizumab experienced significantly fewer asthma exacerbations. However, clinical applications are limited by its high cost and currently it cannot be considered a first-line treatment, but rather is used as a more personalised therapy approach for patients with uncontrolled disease.

Besides allergic rhinitis, upper respiratory tract infections account for a large part of the burden associated with asthma and COPD exacerbations. Current available treatment options remain limited. It has been hypothesised that, in order to treat virus-induced lower airways exacerbations, there are two therapeutic strategies: targeting either the responsible virus or the patient's immune response [84]. Several antiviral agents have been tested, such as IFN-α at high dose, soluble intercellular adhesion molecule (ICAM)-1, capsid-binding

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agents and hRV 3C protease inhibitors [85–87]. All of these agents are in different stages of development in pre-clinical or clinical trials. However, their efficacy in treating virus-induced lower airways exacerbations has not been demonstrated so far. Moreover, vaccination against hRV has currently failed to prevent asthma and COPD exacerbations because of the wide variety of serotypes of hRV.

Preventing the inflammatory reaction caused by hRV infection is another therapeutic strategy. In several studies, corticosteroids failed to treat asthma and COPD acute exacerbations [88, 89]. Even after doubling the dose of inhaled corticosteroids during asthma attacks, the results are unsatisfactory [90–92]. In COPD exacerbations, steroids failed to efficiently improve lung FEV1 or significantly shorten the duration of hospitalisation [93]. New therapeutic agents are currently in the experimental stages of development. NF-κB is known to be involved in virus-induced upregulation of ICAM-1. Moreover, NF-κB activates a large number of pro-inflammatory mediators involved in hRV infection [94].

Nonallergic, noninfectious rhinitis patients have so far not been extensively studied or well characterised. An association between upper and lower airways disease in nonallergic, noninfectious rhinitis patients has been established for occupational rhinitis and asthma. However, occupational asthma is more studied than occupational rhinitis. It has been demonstrated that many of the causative agents of occupational asthma are also able to induce rhinitis. The prevalence of rhinitis in asthma caused by high- or low-molecular-mass agents is equal; however, more severe rhinitis symptoms are documented in the high-molecular-mass group [95]. Moreover, in this group, rhinitis often precedes the onset of asthma [20]. Occupational rhinitis is considered a risk factor for asthma development, especially during the year following rhinitis notification [96]. However, the underlying mechanisms of how respiratory symptoms in upper, lower or global airways occur in occupational disease remain enigmatic. Occupational airways disease is considered a unique clinical entity, as discontinuation of exposure to the causative agents results in resolution of airway symptoms.

Impact of controlling sino-nasal inflammation on the bronchi

Sino-nasal inflammation is a complex disease with several variants caused by different cellular and molecular mechanisms. It is considered multifactorial in origin with genetic, local and systemic immunological factors contributing to environmental, microbial and even iatrogenic effects in the development and chronicity of the disease [2]. Current guidelines for treatment tend to divide CRS into forms with and without polyps [5]. Guidelines are based on the severity of the disease, whereas modified treatment strategies for children have been incorporated into the recent updated version [5, 22]. There are a large number of different treatment modalities in the literature for treating CRS, but most of these treatment options do not have proven efficacy in prospective randomised placebo-controlled double-blind trials. Apart from nasal irrigation, douching, corticosteroids and antibiotics, other treatment options are lacking evidence of benefit [5]. The general therapeutic approach for CRS consists of medical treatment, while surgery is reserved for cases of uncontrolled disease despite maximal medical therapy [5, 97].

The effect of CRS treatment (medical or surgical) on asthma has recently been much more studied and is far less controversial than in the past. However, inconsistency still exists and therefore well-designed trials are warranted to shed more light in this field. Endoscopic sinus surgery (ESS) for CRS relieves sino-nasal inflammation and symptoms but may also reduce bronchial symptoms, resulting in a reduction of medication use for bronchial asthma [98–102]. In one study, 90% of asthmatic patients reported better asthma control after ESS for a mean follow-up period of 6.5 years in terms of reduction of medication use for asthma and the number of asthma attacks [25]. Additionally, in children with CRS and asthma, ESS improves the clinical course of asthma, the number of asthma hospitalisations and schoolday absenteeism [103]. Lung function in asthmatic patients with CRS was reported to benefit from ESS in several studies [98, 102, 104]. Moreover, early surgical intervention in the course of medically refractory CRS has gained ground concerning the time of surgery. Data from a recently published retrospective analysis show that a prolonged pre-operative period is significantly correlated with asthma comorbidity [105]. Overall, as the time from diagnosis to surgery lengthens, patients experience worsening of their respiratory condition, while post-operatively healthcare expenditure and needs are maintained at high levels [105–108]. However, not all studies show beneficial effects of ESS on asthma [99, 101, 103, 109]. This inconsistency is related to the heterogeneity of these studies, the small sample sizes and the different parameters studied.

Concerning CRSwNP with concomitant asthma after ESS, a significant improvement in lung function was noted accompanied by a reduction of systemic steroid use [110]. However, this was not the case in AERD patients. In a small series of CRSwNP patients, sinus surgery did not change the asthma status [111]. Nevertheless, QoL and nasal breathing improved in most patients. Data on the effects of surgery for CRSwNP on asthma mostly point towards a beneficial effect of surgery on different parameters of asthma. In a prospective randomised trial, the effect of ESS followed by fluticasone propionate nasal drops 400 µg twice daily was investigated in 68 asthmatic subjects with CRSwNP [112]. The study was conducted over 21 weeks and the effects of ESS on nasal and lower airways parameters were examined. The authors reported that ESS significantly improved mean asthma symptoms score, daily peak expiratory flow rate and all of the measured nasal parameters [112]. Batra *et al.* [110] reported a significant improvement in FEV_1 and a reduction in oral corticosteroid use after ESS in 17 patients with CRSwNP and oral corticosteroid-dependent asthma. In a series of 13 patients with CRSwNP and asthma, Uri *et al.* [111] reported that ESS did not improve the asthma state in patients with massive nasal polyposis. However, there was a significant decrease in oral corticosteroid and bronchodilator inhaler usage. In a subgroup of 35 CRSwNP patients with asthma, Ragab *et al.* [113] reported that ESS had a subjective and objective tendency for asthma improvement in a prospective randomised trial. Thus, although the study results are not always consistent, overall it would appear that ESS has a positive effect on asthma in CRSwNP.

Interestingly, outcomes after ESS for CRS are significantly worse in the presence of lower airways disease compared with the nonasthma group [98, 100]. The same is also reported for patients with aspirin-intolerant asthma [110, 114]. In contrast, other authors have found that asthma may not have a negative impact on symptomatic outcome after primary or revision ESS [115–117]. Kennedy [118] reported that asthma did not affect the outcome after ESS in a series of 120 patients when those with equally severe sinus disease were compared. However, asthma did adversely affect the outcome after ESS in patients with the most severe disease. In contrast, a recent systematic review analysed the effect of upper airway intervention in a subpopulation of patients with coexisting CRSwNP and asthma and did not find marked differences between outcomes after ESS or medical treatment with montelukast, omalizumab or erythromycin [119].

To date, there has been a lack of well-conducted clinical trials analysing the effects of different medical treatments in patients with concomitant asthma and CRS. Particularly in patients with CRSwNP and asthma, the most used treatments are macrolide antibiotics, anti-leukotrienes and monoclonal antibodies. Low-dose macrolides have been used as a long-term antibiotic treatment in CRS. Their efficacy has been reported in nonrandomised noncontrolled studies [120–123] and may be attributable not only to their antibacterial but also to their anti-inflammatory and glucocorticosteroid-sparing action. In a randomised controlled prospective trial of 90 CRS patients who failed initial treatment with intranasal corticosteroids and nasal lavage, continued medical therapy and surgery was compared using a 3-month course of erythromycin *versus* ESS [113]. Both the medical and the surgery groups had improved asthma at the 12-month follow-up. Moreover, the continued medical therapy group (erythromycin group) had a greater improvement in objective pulmonary function tests [113]. A double-blind placebo-controlled crossover trial and an uncontrolled prospective trial were done studying the effect of montelukast treatment in patients with CRS and concomitant asthma [124, 125]. Although follow-up for both trials was restricted, significant improvements in nasal and pulmonary symptoms as well as in asthma medication use were reported for both trials. However, this was not the case for nasal and pulmonary function tests.

Following the current evolution in endotyping, more personalised treatments based on the underlying inflammation are likely to be considered in the future. As already mentioned, increased local production of IgE antibodies appears to be functional and involved in the regulation of chronic inflammation for CRSwNP patients [126]. Gevaert *et al.* [127] recently published the first double-blind randomised controlled trial investigating the clinical efficacy of omalizumab in patients with CRSwNP and comorbid asthma. The study reported a significant decrease in total polyp score after treatment with omalizumab. Moreover, omalizumab, but not placebo, caused improvements in nasal and asthma symptom scores compared with baseline scores, irrespective of patient atopic status. Previous case reports and case series also suggested the beneficial effect of omalizumab in patients with CRSwNP and comorbid allergic asthma [128–130]. More randomised controlled trials are needed for further evaluation of the benefits to the upper and lower airways. However, given the cost of targeted treatments with monoclonal antibodies, the use of omalizumab should be restricted to patients with CRSwNP and asthma when previous ESS and maximal conventional medical treatment are not able to control upper airways symptoms.

In contrast to sino-nasal inflammation and asthma, very little is known about the interaction between CRS and COPD. This is paradoxical as the majority of COPD patients treated in an academic respiratory department report sino-nasal symptoms. Several pro-inflammatory mediators are increased in the nasal lavage of patients with COPD [131]. Moreover, the overall impairment of the QoL in COPD is associated with the presence of sino-nasal symptoms [131]. Interestingly, a large number of patients with bronchiectasis have rhinosinusitis symptoms, radiological abnormalities on CT scans and reduced smell capacity [131]. Recently, sino-nasal symptoms in COPD were linked with health status impairment and concomitant CRS was associated with treatment failure at exacerbation [132]. Further studies are warranted to elucidate the impact of upper airway treatment in patients with COPD and bronchiectasis.

Current gaps in our understanding of the sino-nasal–bronchial interaction

The sino-nasal–bronchial interaction is still not fully understood, complicating our clinical approach to individuals with upper and/or lower airways pathology. There is a lack of biomarkers to predict if and when allergic rhinitis will develop in clinical asthma. In patients with CRSwNP and asthma, there is no evidence whether medical treatment and/or upper airways surgery is beneficial for bronchial diseases. Alternatively, physicians may need to examine the upper airways in patients with asthma or COPD, since the impact of asthma and/or COPD on upper airways inflammation is not fully elucidated. A simple, validated questionnaire can be a helpful tool to investigate the absence/presence of rhinosinusitis [133], emphasising the need for a closer collaboration between different specialists to design novel therapeutic strategies aimed at obtaining the best outcomes in both parts of the airway. See van der Meer and ten Brinke [134] and Fokkens and Hellings [135] elsewhere in this *ERS Monograph* for a comparison of the perspectives of the chest physician and ENT specialist with regard to nasal polyposis and asthma.

One of the current gaps in our understanding of the interaction between the sino-nasal and bronchial systems is the lack of knowledge about the underlying mechanisms contributing to upper and/or lower airways diseases. Epithelial barrier deficiencies may be a common factor in the development of upper and lower airways diseases. The airway epithelium is the first line of defence against allergens and pathogens. Recently, barrier defects have been demonstrated to be part of the pathology of asthma [136], CRS [137] and allergic rhinitis [138]. As a consequence, allergens and/or pathogens have easier access to the submucosal region and thus contribute to chronicity and severity of the different diseases. It would be extremely interesting to evaluate bronchial barrier function in allergic rhinitis or CRS and *vice versa* to gain more insight into the link between upper and lower airways diseases.

Lastly, there is an urgent need for noninvasive tools to evaluate upper and lower airways inflammation. One promising method is measuring nitric oxide (NO). In asthma, exhaled NO is a well-established, noninvasive method for the assessment of active, mainly Th2-driven airway inflammation [139]. NO measurements have long been used as a valued tool in the diagnosis and monitoring of corticosteroid-sensitive asthma [140]. More recently, NO measurements have been evaluated in several other (lower) respiratory, allergic, infectious and/or immunological conditions [141], although further studies are warranted to evaluate their usefulness in upper airways inflammation.

Future challenges in the clinical approach to upper and lower airways pathology

The concept of “one airway, one disease” is increasingly being used to understand both upper and lower airways pathology. However, many questions remain unanswered, such as which factors play a role in allergic phenotypes. Both intrinsic and extrinsic factors are thought to orchestrate the induction of symptoms. Indeed, intrinsic factors, such as breathing patterns, organ susceptibility and genetic predisposition, are probably associated with bronchial symptoms in patients with CRS. Extrinsic factors, such as the microbiome, the type of allergen and the presence of occupational factors, may all contribute to the complex picture of global airway disease.

An awareness of nasal symptoms in patients with lower airways inflammation, and *vice versa*, is probably the best therapeutic and diagnostic approach for the future. Chest physicians and ENT specialists should together examine and interpret clinical abnormalities of the upper and lower airways to fully understand the concept of “united airways disease”. Anterior rhinoscopy and nasal endoscopy should be combined with lung function tests in patients with any chronic airway inflammatory disorder. Lastly, there is an urgent need to define the diagnostic and therapeutic value of biomarkers to evaluate airway inflammation.

Conclusions

For a long time, the concept of "united airways disease" was neglected. Despite all emerging data showing common epidemiological and pathophysiological features between the nose and the bronchi, and the positive effect of optimal care treatment of one part of the airway on the other, routine clinical experience still shows that a significant portion of patients with lower airways disease are deprived of proper care of the upper airways. Rhinitis is a well-established risk factor for asthma development and persistence, while allergic rhinitis management has been shown to result in alleviation of asthma symptoms. Similarly, >50% of patients with CRS have either asthma or bronchial hyperreactivity when challenged with methacholine in different studies.

In view of this interaction between the upper and lower airways, the different medical and clinical specialists should work closely with each other to fully understand the underlying mechanisms of "united airways disease", to develop diagnostic tools for evaluation of airway inflammation, to define new therapeutic targets to halt the progression and reduce the socioeconomic burden of this pathology, and overall to predict who might benefit from a referral to an ENT specialist to optimise the upper airways treatment, taking into account preventative, predictive and personalised care in the approach.

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United airways paradigm in guidelines and clinical practice

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Although some guidelines note the united airways concept, only one provides useful information to aid the practising clinician in diagnosing and treating the patient with combined disease. There is one QoL document for rhinitis and asthma, but, as yet, none published for rhinosinusitis and asthma. This lack of an approach to all of a subject's symptoms may hinder concordance and could predispose to adverse events if medication is prescribed from two sources. A proposal is made regarding future treatment for united airways patients.

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The respiratory tract is conventionally divided into upper and lower areas, with the division at the laryngeal level. ENT surgeons predominantly treat the upper part, and chest physicians the lower. Yet normally air passes through the nose to ventilate the lungs, which allows for filtration, warming and humidification of inspired air and protection of the lower airways. Disorders of the nose, paranasal sinuses, nasopharynx and larynx can therefore have an impact on the bronchi and lungs, and, conversely, lower respiratory tract problems can affect the upper airways. There are also conditions, such as CF or immunodeficiency, that typically affect the whole system. Thus, it makes sense to consider the whole airway in every patient, but to what extent is this approach reflected in current guidelines?

Rhinitis guidelines

The Allergic Rhinitis and its Impact on Asthma (ARIA) document [1] was the first to state clearly the link between rhinitis and asthma. However, having established this and provided questions to enable diagnosis of both rhinitis and asthma, the subsequent advice regarding clinical manifestations, diagnosis and treatment concerns rhinitis alone. Approaches to the treatment of asthma are largely unexplored.

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More extensive combined advice is found courtesy of the International Primary Care Respiratory Group (IPCRG). Two papers in 2006 dealt with the diagnosis and management of diseases of both upper and lower respiratory tracts in primary care. Levy *et al.* [2] used a symptoms-based approach, and original questionnaires and diagnostic guides were included to help the primary care clinician proceed systematically through the diagnostic process. Price *et al.* [3] stated that "the association between the upper and lower airways has been recognised for almost 2000 years. Epidemiological data suggest that most asthma patients also suffer from allergic rhinitis, and that both diseases share similar trigger factors and pathophysiology." This latter IPCRG guideline accords with the ARIA guidelines in highlighting the aims of treatment and classifying allergic rhinitis according to severity and duration. It is unique in covering the management of coexisting allergic rhinitis and asthma.

Paediatric guidelines produced by the European Academy of Allergy and Clinical Immunology [4] also note the interaction between rhinitis and asthma, plus the fact that rhinitis is a risk factor for the development of asthma [5, 6] and that the latter may be preventable by treating allergic rhinitis with allergen-specific immunotherapy. The possible exacerbation of asthma by nasal disease is remarked upon, with asthma severity and the presence of allergic rhinitis both increasing the risk of asthma hospitalisation in a cross-sectional study involving 126 asthmatic children and adolescents [7]. The combination of a viral upper respiratory tract infection plus exposure to relevant allergen(s) in sensitised asthmatic children synergistically increased the need for emergency care [8]. This Task Force document also provides guidance on identifying asthma in a box entitled "Recognising comorbidities of rhinitis in childhood" and warns against mistaking post-nasal drip-induced cough for asthma.

Rhinosinusitis guidelines

The evidence-based European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS2012) is an update of two previous papers [9]. It contains chapters on definitions and classification and uses the terms CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP) to note differences in management and associations of these two pathologically distinct subgroups.

There is a subchapter on the relationship between upper and lower airways, in which the following is noted [9]: "Due to its strategic position at the entry of the airway, the nose plays a crucial role in airway homeostasis. By warming up, humidifying and filtering incoming air, the nose is essential in the protection and homeostasis of the lower airways. The nose and bronchi are linked anatomically, are both lined with a pseudo-stratified respiratory epithelium and equipped with an arsenal of innate and acquired immune defence mechanisms." Moreover, "in chronic sinus disease with nasal polyps (NP), total blockage of nasal breathing may occur, hence bypassing nasal functions that may be relevant in preventing lower airway disease. It is however evident that the nasobronchial interaction is not restricted to bronchial repercussions of hampered nasal air conditioning. Nose and bronchi seem to communicate via mechanisms such as neural reflexes and systemic pathways."

The document, which is more of a review than guidelines, also notes that bronchoconstriction, which occurs rapidly following exposure of the nose to cold air, facial

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cooling and nasal allergen challenge [10–12], is presumably neurally mediated. Additionally, many upper airways inflammatory disorders have a systemic immunological component involving the bloodstream and bone marrow [13], allowing for knock-on effects at distal, lower airways mucosal sites. Genetic factors may also play a role in the manifestation of nasal and/or bronchial disease, *e.g.* in CF and α_1-antitrypsin deficiency [14].

EPOS2012 also explores underlying conditions that may impact on the whole airway [9].

CRS and asthma

The EPOS2012 guidelines note that the strong association between CRS and asthma was confirmed recently, with 50% of CRS subjects having asthma in some European centres [9]; in nonatopic individuals this was typically late-onset asthma [15]. Even nonasthmatic patients with CRS often show bronchial hyperresponsiveness on methacholine challenge [16]. Sinus CT scans show sino-nasal inflammatory opacification in the majority of patients with severe asthma [17, 18]. CRSwNP resembles asthma histologically and in the cytokines present in Western subjects; these patients have characteristic eosinophilic inflammation in both sputum and nasal secretions [16, 19]. The association between nasal polyposis and asthma is discussed in more detail elsewhere in this *ERS Monograph* [20–22].

Endoscopic sinus surgery (ESS) for CRS may improve asthma symptoms and reduce medication use [23–27], even in children [28], although not all studies report this positive effect [29]. The effects on pulmonary function are disputed with both positive [26, 30, 31] and negative [23, 25, 28] reports. Paediatric studies suggest remission of asthma in many subjects following treatment of CRS, but lack controls and are insufficiently robust [32, 33].

Lower airways disease may have a negative impact on the outcome of ESS [24, 31], particularly in patients with AERD [34–36]. Ragab *et al.* [37] published the first randomised prospective study of surgical compared with medical therapy of patients with CRSsNP/CRSwNP and asthma on asthma outcomes, and found equivalent results, although medical management was superior to surgery in the subgroup of subjects with CRSwNP. Both regimens were associated with subjective and objective improvements in asthma. The degree of improvement in upper airways symptoms correlated with that in asthma symptoms and control.

CF and rhinosinusitis

Most CF sufferers have upper respiratory tract inflammation, with one-third having nasal polyps. Some CRS patients are heterozygotes with one mutation of the CFTR gene [38]. Organisms cultured from the sinuses are also found in bronchoalveolar lavage [39], with pneumococci often appearing first in the upper airway. Sinus surgery in CF subjects may provide some improvement in lung function [40], but prospective studies on the effects of ESS on lower airways function in CF are needed. A more detailed discussion of CRS in CF patients is given by Hamilos [41] elsewhere in this *ERS Monograph*.

COPD, bronchiectasis and rhinosinusitis

Sino-nasal symptoms occur in COPD patients and are proportional to the reduction in their QoL [42, 43]. Levels of eotaxin, granulocyte colony-stimulating factor and IFN-γ were higher in nasal fluid in COPD patients than in controls [43]. Patients with bronchiectasis also frequently have rhinosinusitis symptoms [44], sinus CT scan abnormalities [45] and poor olfaction [46]. The impact of upper airway treatment in such patients needs further study. More detailed discussions of these topics are given by HURST and HUERTA GARCIA [47] (COPD) and RAIDT and WERNER [48] (non-CF bronchiectasis and PCD) elsewhere in this *ERS Monograph*.

Aspirin-exacerbated respiratory disease

The natural history of AERD shows that the problem usually begins in adult life, initially with rhinitis (sometimes with a flu-like infection), followed by the development of chronic intractable rhinosinusitis with nasal polyps and the appearance of late-onset asthma [49]. The aspirin/cyclooxygenase-1 NSAID hypersensitivity appears at some stage and can be life-threatening. It is associated with severe, difficult-to-treat, eosinophilic inflammation of the upper and lower airways, with rapid polyp recurrence after sinus surgery, and with asthma, which may necessitate ongoing oral corticosteroid therapy.

EPOS2012 recommends diagnosis using nasal, bronchial or oral challenge, but does not provide references to aid this [9]. According to the document, management of asthma and rhinosinusitis in AERD patients should include nasal douching, high doses of topical corticosteroids to both upper and lower airways, often in combination with long-acting β_2-agonists in the lower airways, antibiotics and occasional bursts of oral corticosteroids, but specific measures for AERD should also be considered. These include antileukotrienes, which may be effective in some AERD patients.

Patients with AERD respond less well to surgical intervention [35, 36, 50–52]. Repeated doses of oral aspirin can achieve a biochemical desensitisation after the initial adverse reaction [53–57] and may have a beneficial effect throughout the airways. However, the dose of aspirin used is not standardised, with the various authors recommending between 100 and 1600 mg daily. Studies of the use of aspirin desensitisation post-surgery are required. Intranasal challenge using soluble lysine aspirin is suitable for diagnosis [58], and prolonged therapy may reduce the recurrence rate for nasal polyps and reduce asthma exacerbations [59–62].

Monoclonal antibodies targeting IL-5 [63], IgE [64] or the IL-4 receptor α-subunit [65], which may have a role in hard-to-control CRS plus asthma, especially in AERD subjects, are likely to be included in updated versions of the EPOS guidelines.

Immunodeficiencies

EPOS2012 notes that patients presenting to their primary care physicians or otorhinolaryngologists with recurrent ARS or CRS may have an underlying primary immunodeficiency [9]. Figures from tertiary centres have suggested that up to 50% may have T-lymphocyte dysfunction [66], 20% low immunoglobulin levels and 10% common variable immunodeficiency [66, 67]. However, there is significant selection bias in these figures and the nature of the CRS (with or without polyps) is not explained; there is no mention of whether there were accompanying chest problems.

Patients presenting to immunologists with a variety of infections may have respiratory problems as part of their clinical picture. Common variable immunodeficiency presents with CRS in 36–78% of sufferers [68, 69]. Recurrent ARS was present in 41% and CRS in

40% of a cohort of primary immunodeficiency subjects [70], while 77% of patients with a decreased response to pneumococcal vaccination had rhinosinusitis [71].

The delay between presentation and definitive diagnosis of primary immunodeficiency ranges from 4.7 to 15 years [68, 72, 73]. The upper airways findings do not correlate with pulmonary imaging and most commonly include mucosal thickening; bone sclerosis and polyposis are less common [74].

The clinical benefit to CRS of treatment for IgG deficiency (prophylactic antibiotics and/or intravenous immunoglobulin) is unproven, although survival is increased and life-threatening infections reduced [68]. Surgery for patients with primary immunodeficiency has not been studied thoroughly [75].

Immunological investigation for children with recurrent respiratory tract infections and in adults with multiple system infections, such as otitis media, bronchitis or pneumonia, or those that fail standard medical and surgical treatments for CRS is recommended.

Acquired immunodeficiencies secondary to transplant immunosuppression, diabetes mellitus, medications, malignancies or human immunodeficiency virus present with a variety of rhinosinusitis conditions, including fungal forms, such as acute invasive fungal rhinosinusitis and even fungus balls. The associated lower respiratory tract manifestations are not discussed in EPOS2012 [9].

Vasculitis

The EPOS2012 document mentions this group of devastating conditions only briefly [9]: "Autoimmune vasculitides such as Wegener's granulomatosis and Churg–Strauss syndrome or sarcoidosis may involve the nose and sinuses and on rare occasions may present acutely. The presence of other suggestive symptoms and an atypical clinical course can alert the clinician to alternative diagnoses."

Allergic fungal rhinosinusitis

The allergic fungal rhinosinusitis (AFRS) diagnostic criteria initially described by Bent and Kuhn [76] are shown in table 1. In fact, type I hypersensitivity and characteristic CT findings are the only factors unique to AFRS, as opposed to other forms of CRS. AFRS patients also tend to be younger, African-American and suffer significant bone erosion/expansion [78–80]. Total IgE, and antifungal IgE and IgG antibodies are elevated more than in other forms of CRSwNP in some [81] but not all [78, 82–84] reports.

A possible connection with allergic bronchopulmonary aspergillosis (ABPA) is not mentioned in EPOS2012 [9]. The criteria for this diagnosis are also shown in table 1 [77]. The 2013 ABPA working group paper from which these diagnostic criteria are quoted includes a section on allergic fungal sinusitis as a comorbidity in some ABPA patients [77].

Asthma guidelines

The GINA 2015 report [85] and 2017 update [86] include several references to the upper airways. With regard to phenotyping asthma, reference is made to the fact that allergic

Table 1. Criteria for allergic fungal disease in the upper and lower respiratory tracts

Upper respiratory tract: Bent–Kuhn criteria for allergic fungal sinusitis
- Nasal polyposis
- Fungi on staining
- Eosinophilic mucin without fungal invasion into sinus tissue
- Type I hypersensitivity to fungi
- Characteristic radiological findings with soft tissue differential densities on CT scan

Lower respiratory tract: criteria for the diagnosis of ABPA
- Predisposing conditions
  - Bronchial asthma
  - CF
- Obligatory criteria (both must be present)
  - Elevated serum IgE levels against *Aspergillus fumigatus* ($>0.35\ \text{kUA}\cdot\text{L}^{-1}$) or immediate cutaneous hypersensitivity to *A. fumigatus* antigen (positive type I *Aspergillus* skin test)
  - Raised serum total IgE levels ($>1000\ \text{IU}\cdot\text{mL}^{-1}$)[#]
- Other criteria (at least two of three)
  - Presence of precipitating (or IgG) antibodies against *A. fumigatus* in serum
  - Peripheral blood eosinophil count $>500\ \text{cells}\cdot\mu\text{L}^{-1}$ (may be historical)
  - Thoracic imaging findings consistent with ABPA[¶]

ABPA: allergic bronchopulmonary aspergillosis. [#]: an IgE value $<1000\ \text{IU}\cdot\text{mL}^{-1}$ may be acceptable, if all other criteria are met; [¶]: the features on thoracic imaging consistent with ABPA may be transient (*i.e.* fleeting opacities, toothpaste/gloved finger opacities, tram-track opacities, consolidation or nodules) or permanent (*i.e.* bronchiectasis, parallel lines, ring shadows or pleuropulmonary fibrosis). Neither set of criteria considers the other part of the respiratory tract. Information from [76, 77].

rhinitis, as well as other atopic diseases, is associated with allergic asthma, typically asthma with onset in childhood or adolescence. Notably, there is no mention of CRS being associated with adult-onset, typically nonatopic disease. Conversely, rhinosinusitis is identified as a risk factor for poor asthma outcomes, and the reader is alerted to consider this comorbidity, among others, in cases of uncontrolled asthma. Allergic rhinitis is noted as a comorbidity in asthmatic children aged 6–11 years. The upper airways are also highlighted as a source of one differential diagnosis for asthma, described as “chronic upper airway cough syndrome”. Vocal cord dysfunction is also noted as a differential diagnosis. A subsection in the 2016 document entitled “Rhinitis, sinusitis and nasal polyps” describes the link between upper and lower airways and the high frequency of rhinitis seen in asthmatic subjects, followed by succinct definitions of each modality [86]. Reference is made to the ARIA guideline [1], plus a mention that, in population-based studies, if not in formal prospective randomised controlled trials, treatment of rhinitis appears to have a positive impact on asthma control. Reference is made to the fact that CRS is associated with more severe asthma, particularly CRSwNP. A subsequent section on AERD describes the association with nasal polyposis, severe asthma and aspirin hypersensitivity seen in some patients. CRS is first in the list of comorbidities that should be screened for in individuals with severe asthma.

The British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS-SIGN) 2016 guideline [87] has rather less reference to the upper airways. In working towards a diagnosis of asthma, “personal/family history of other atopic conditions (in particular, atopic eczema/dermatitis, allergic rhinitis)” should be noted. Rhinitis is listed among differential diagnoses for asthma in adults (as is vocal cord dysfunction), but not in children. It is stated that patients with asthma often have rhinitis, with the most effective therapy being intranasal corticosteroids, but that a positive effect of intranasal corticosteroids on asthma has not been seen in double-blinded placebo-controlled trials. Aspirin-intolerant asthma is mentioned, but there is no mention of nasal polyposis or CRS. Unlike the GINA guideline [86], there is no mention of the upper airways in the section on "Difficult asthma". There is no mention of rhinitis in the section on "Occupational asthma", although the development of rhinitis typically pre-dates the development of asthma in cases of IgE-mediated occupational asthma [88].

The European Respiratory Society/American Thoracic Society guideline on severe asthma [89] mentions, in a section on phenotyping asthma, that late-onset severe asthma may be associated with "persistent eosinophilic inflammation, nasal polyps and sinusitis and often aspirin sensitivity". In the list of comorbid conditions, "rhinosinusitis/(adults) nasal polyps" is listed first, followed by a note that "evidence for rhinosinusitis has been reported to be as high as 75–80%" in severe asthmatic subjects. However, management of this comorbidity is not discussed.

The US National Heart, Lung and Blood Institute guidelines 2007 [90] suggest evaluating for comorbid conditions, including rhinitis/sinusitis, when asthma cannot be well controlled. The guidelines state that "those persons who treat asthma need to concern themselves with the best therapy for the upper airway to optimize overall therapy for their patients". Mention is made of the similarity between the upper and lower airways with regard to pathology, including the effects of provocation tests of the nose on the lungs and *vice versa* [91, 92], and of studies suggesting a benefit of treating allergic rhinitis on prevention of emergency visits for asthma [93, 94], but with a caveat about their limitations. Overall, grade B evidence is given for the recommendation that "clinicians evaluate patients who have asthma regarding the presence of rhinitis/sinusitis diagnosis or symptoms".

Thus, each guideline mentions, to a greater or lesser extent, the need to consider the upper airways in asthmatic patients. The absence of sufficient, well-conducted prospective randomised controlled trials of the effect of intranasal steroids in patients with concurrent allergic rhinitis and asthma means that none of the guidelines places an emphasis on treating the upper airways as part of routine management in asthma. (However, it should be noted that a meta-analysis of the effects of intranasal corticosteroids on asthma outcomes in allergic rhinitis did conclude a positive effect, albeit most conclusively in patients not taking inhaled corticosteroids [95]). Similarly, the absence of equivalent studies in patients with CRS and asthma means an absence of a clear recommendation here.

The "middle airway"

Both the GINA [86] and BTS-SIGN [87] guidelines identify vocal cord dysfunction as an important differential diagnosis for asthma. While the larynx is the province of ENT surgeons rather than chest physicians, in the authors' experience, patients with vocal cord dysfunction or other types of dysfunctional breathing involving the larynx (sometimes referred to as intermittent laryngeal obstruction) are frequently treated for asthma and seen by chest physicians. One of the benefits of running a clinic with expertise on both upper and lower airways is the ability to diagnose these patients with direct laryngoscopy, albeit sometimes requiring some form of provocation procedure, instead of relying on suggestive findings on spirometric flow–volume loops [96].

QoL measurements

Often, the two levels of the respiratory tract are dealt with separately, in different clinics, by ENT surgeons and chest physicians, with no consideration being given to the importance of the other part. Patients themselves do not always realise that their problems are linked.

One way forward would be the use of a QoL instrument combining both elements. Global evaluation of patients should include the measurement of health-related QoL (HRQoL) in addition to clinical findings and objective measurements [97]. The impact of a disease on QoL is self-assessed by the patient using validated instruments. Assessing the patient's subjective point of view offers a more comprehensive description of the impact of a disease and its treatment upon his or her life [98]. This is particularly relevant in chronic disease, where the primary goal of treatment is to improve functioning in daily life and to achieve the highest possible level of well-being.

Generic QoL questionnaires are applicable to all health conditions, while specific ones are restricted to a particular disease, a selected population (*e.g.* adults, children, the elderly), or a specific function or problem. Although more sensitive than the generic ones, specific QoL instruments do not allow comparison between different diseases. Frequently, specialised individual questionnaires are used for upper respiratory tract symptoms, but patients are not asked about their asthma or other chest symptoms. The reverse occurs in asthma/chest clinics. Yet the majority of asthma patients have some form of upper airways problem, which usually corresponds in severity concomitantly with the lower airways problem [99]. Exacerbations of asthma are most often caused by viral infections that originate in the nasopharynx [100] and which are more severe in the presence of pre-existing inflammation [101]. Furthermore, there is evidence that treatment of the nose can improve symptoms in the chest [102, 103].

There are several specific instruments that assess HRQoL in rhinoconjunctivitis or in asthma, but instruments evaluating rhinitis and asthma together are rare. An Italian group developed and validated a specific QoL questionnaire for adult patients with rhinoconjunctivitis, asthma or both [104]. They used 42 items generated from a literature review and clinical experience to cover the various symptoms and problems. These were shown to 148 consecutive outpatients: 46 suffering from asthma, 53 from rhinoconjunctivitis and 49 from both. The patients were asked which items were relevant to them and how important each was on a four-point scale (1=not important; 4=very important). 12 items were consequently rejected. For validation of the new questionnaire (Rhinasthma), it was presented to 104 patients (42 with rhinoconjunctivitis alone and 62 with asthma and rhinoconjunctivitis) together with the Short Form Survey (SF)-36. Rhinasthma differentiated patients with upper respiratory problems only from those with both rhinitis and asthma, and showed good reliability [105].

Subsequently a new adaptation of the Rhinasthma questionnaire for English-speaking populations was tested for validity and performance [106]. Five discrete item clusters corresponding to the domains of nasal (five items), eye (four items), respiratory (five items), activity restriction (nine items) and treatment burden (five items) were identified. Two items were removed because of poor item–cluster correlations.

HRQoL impairment, as measured by Rhinasthma, was greater in patients with both asthma and rhinitis than in those with either alone. Rhinasthma correlated significantly ($p<0.05$) with the EQ-5D (EuroQoL five dimensions questionnaire), SF-12 and Marks Asthma

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Quality of Life Questionnaire. Poorer Rhinasthma HRQoL was associated with significantly ($p<0.05$) increased odds of both asthma- and rhinitis-related disability, even after taking into account physical health status as measured by the SF-12.

There is a need for a combined rhinosinusitis and asthma questionnaire. There is currently no such existing document. Although Rhinasthma includes rhinitis and asthma, it omits the elements particular to rhinosinusitis, such as headache, facial pain and ear involvement. Up to now, in the rhinology clinic of one of the authors (G.K.S.) (where the whole respiratory tract is considered), patients have routinely been asked to complete two validated questionnaires at each visit as part of their assessment: the Sino-Nasal Outcome Test (SNOT)-22 for CRS and the Asthma Control Questionnaire (ACQ) for asthma.

In order to simplify the routine for our patients, we have tried combining these two questionnaires into one: the Sino-Nasal Asthma Test (SNAT). This is based on an adaptation of SNOT-22 and ACQ, using analysis of previous patients' completion of these forms to remove rarely ticked and redundant questions. In 192 adult subjects, SNAT showed validity, internal consistency, reproducibility and responsiveness (G.K. Scadding, unpublished data). Using this tool should encourage both patients and their doctors to consider both upper and lower respiratory tract symptoms and signs, and to treat them as necessary in patients with CRS, asthma or both.

Patient satisfaction, concordance and adherence with therapy

Approximately one-third to one-half of therapy is not undertaken correctly or even at all. Factors behind this nonadherence, which can be deliberate or unintentional, are complex and appear not to relate to age, sex, race, education, intelligence, marital status or income. Indeed, adherence rates vary within the same patient at different times [106]. However, there is evidence that the complexity of treatment and the cost of medicines can adversely influence their use [107]. This is a particular problem in subjects with two conditions, such as rhinitis and asthma, requiring separate treatment at two sites. Additionally and unsurprisingly, belief in the necessity of treatment affects its use, with symptoms provoking adherence [108]. This is also a problem in conditions such as rhinitis and asthma where low-grade inflammation can persist and needs controlling, but presents with little in the way of acute symptoms and is consequently ignored or deprioritised by patients.

Improvement in adherence requires interaction with the individual patient: understanding their perceptions of the disease and its treatment, as well as relevant practical issues that might help or hinder adherence [109]. Being seen and treated at two different clinics or hospitals is likely to confuse the patient and reduce concordance, especially if the messages received (*e.g.* your cough is due to a chest condition *versus* your cough is caused by post-nasal discharge) are contradictory.

There is thus a need for high-quality interaction, with a questioning of the knowledge and beliefs of the patient, and subsequent explanation from healthcare professionals, in a joint clinical setting where all aspects of their airway problems are considered. No guideline exists for setting up such an environment, but the provision of a knowledgeable nurse or pharmacist to whom the patient can talk freely may be very helpful. Failing that, a daily reminder by short message service ("SMS") on a mobile phone improved adherence to intranasal corticosteroid therapy in a recent study [110].

Simplification of the drug regimen could also be beneficial. Unfortunately, there is no provision of a corticosteroid that can be inhaled through the nose to the lungs, treating both sites at once. Some medications benefit both nose and chest; in order of ascending initial cost these are: oral corticosteroids, leukotriene receptor antagonists (LTRAs; *e.g.* montelukast), allergen-specific immunotherapy, anti-IgE and anti-IL-5, as well as, potentially, anti-IL-4 receptor drugs.

Oral corticosteroids

Unfortunately, the adverse effects of long-term high-dose systemic corticosteroids preclude their use except in the most severely affected subjects who are genuinely unresponsive to other treatments. Adherence is a problem, with both overuse and underuse reported. Provision of oral corticosteroids by two separate clinics could lead to adverse effects in an individual patient, especially where communication is poor and/or there is a failure to take charge of monitoring for side-effects.

Leukotriene receptor antagonists

The real-life effectiveness of an LTRA in primary care asthmatic patients was examined in two studies commissioned by the UK Health Technology Assessment Programme [111]. One compared an LTRA and inhaled glucocorticoids as first-line controller therapy, while the second compared an LTRA and a long-acting β_2-agonist as add-on therapy for uncontrolled asthma patients receiving inhaled glucocorticoids. Adherence to an LTRA was better than it was to the other drugs in both trials, with adherence rates that were numerically higher in the first-line controller therapy trial (65% *versus* 41% for an inhaled glucocorticoid) and significantly higher in the add-on therapy trial (74% *versus* 46% for a long-acting β_2-agonist). The asthma outcomes were largely equivalent.

Allergen-specific immunotherapy

The unique benefit of allergen-specific immunotherapy for allergic rhinitis is its capacity to modify the natural history of the disease, inducing lasting clinical tolerance, and reducing the development of new asthma and new sensitisations. It is also effective for house dust mite allergic disease in both the upper and lower airways, with sublingual immunotherapy (SLIT) being cheaper than subcutaneous immunotherapy (SCIT) in one Danish study [112]. Adherence to the therapy is mandatory, as happens for all chronic medical treatment. Concordance with allergen immunotherapy is also problematical. In a review, Incorvaia *et al.* [113] found rates ranging from 44% to 89% for SCIT and from 76% to 97% for SLIT. Kiel *et al.* [114] showed in a real-life study of 6486 patients starting immunotherapy between 1994 and 2009 that only 18% of users reached the minimally required duration of treatment of 3 years (SCIT 23%, SLIT 7%). The median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively ($p<0.001$). Conversely, a study in Germany demonstrated far better concordance, as based on prescription renewal rates, with the greater perseverance of treatment seen in patients on SLIT [115]. Patients most often cite inconvenience, side-effects and poor efficacy as reasons for discontinuing allergy immunotherapy [116].

Demoly *et al.* [117] suggested a need for allergen immunotherapy patient support programmes, with both educational and motivational components in order to improve adherence and help the patient to understand and manage local or systemic adverse events. Important factors include measurement of adherence, reminders, communication channels, and the involvement of caregivers and patient leaders.

Joshi and Dimov [118] noted that we are in an era where technology and social media are omnipresent and influence the daily lives of patients and physicians. Allergists are using these to attempt to improve patient care and compliance with treatment regimens, but there is little information on how these interventions affect patient outcomes. Future studies should be directed not only towards investigating how technology and social media improve the utilisation of and adherence to immunotherapy, but also how effective personal interaction on a regular basis can be.

There is little evidence regarding adherence in combined rhinitis and asthma. One group set out to explore, in general practices in the UK, the association of asthma control with self-reported inhaled corticosteroid adherence, degree of rhinitis and smoking [119]. Poor asthma control (ACQ >1.5) was associated with reported rhinitis (OR 4.62, 95% CI 3.71–5.77), smoking (OR 4.33, 95% CI 3.58–5.23) and low adherence to inhaled corticosteroid (OR 1.35, 95% CI 1.18–1.55). Those with severe rhinitis had the worst asthma control, followed by those with mild rhinitis and then those without rhinitis. This study demonstrated the significant detrimental effect of rhinitis on asthma and the need for its effective treatment.

Conclusions

While there is recognition in both rhinitis/rhinosinusitis and asthma guidelines that patients are often affected by disease in both the upper and lower respiratory tracts, there is often fairly limited information on how to investigate and manage disease at the "other" site. In fact, primary care guidelines give the most detailed advice, although perhaps this is unsurprising given that primary care physicians are responsible for the patient as a whole.

It is the authors' experience that joint clinics, involving both chest physicians/allergists and ENT surgeons, can provide joined-up care for the patient, probably improving outcomes and certainly providing a more convenient service. Notably, nearly all rhinitis patients and many patients with rhinosinusitis do not require surgery, whereas all may benefit from medical treatment. It would make sense for interested physicians (respiratory, allergy, immunology, paediatric) to be better educated in the importance, structure, function, examination and therapy of the upper airways and on when to refer such patients to an ENT surgeon. The combined patient would then receive treatment in one clinic, with a probable increase in adherence and well-being, and reduced costs. Specialist nursing staff also have an essential role in these clinics, including undertaking skin testing, spirometry, peak expiratory and peak inspiratory flow, smell testing and, on occasions, exhaled and nasal nitric oxide measurements. However, perhaps most important is the part they may play in patient education, advising patients on how to use medication devices, self-monitoring and when to seek help. Such multidisciplinary clinics would be well placed to explore new therapies that affect the whole respiratory tract.

Clinical trials of new drugs with the potential to treat both upper and lower airways diseases (recent examples being anti-IgE [57], anti-IL-5 [58] and anti-IL-4 receptor α [59] monoclonal antibodies) should be designed to examine outcomes at both sites. QoL outcomes should also consider both sites, both in trials and in clinical practice. Finally, investigation of adherence and how best to improve it is needed.

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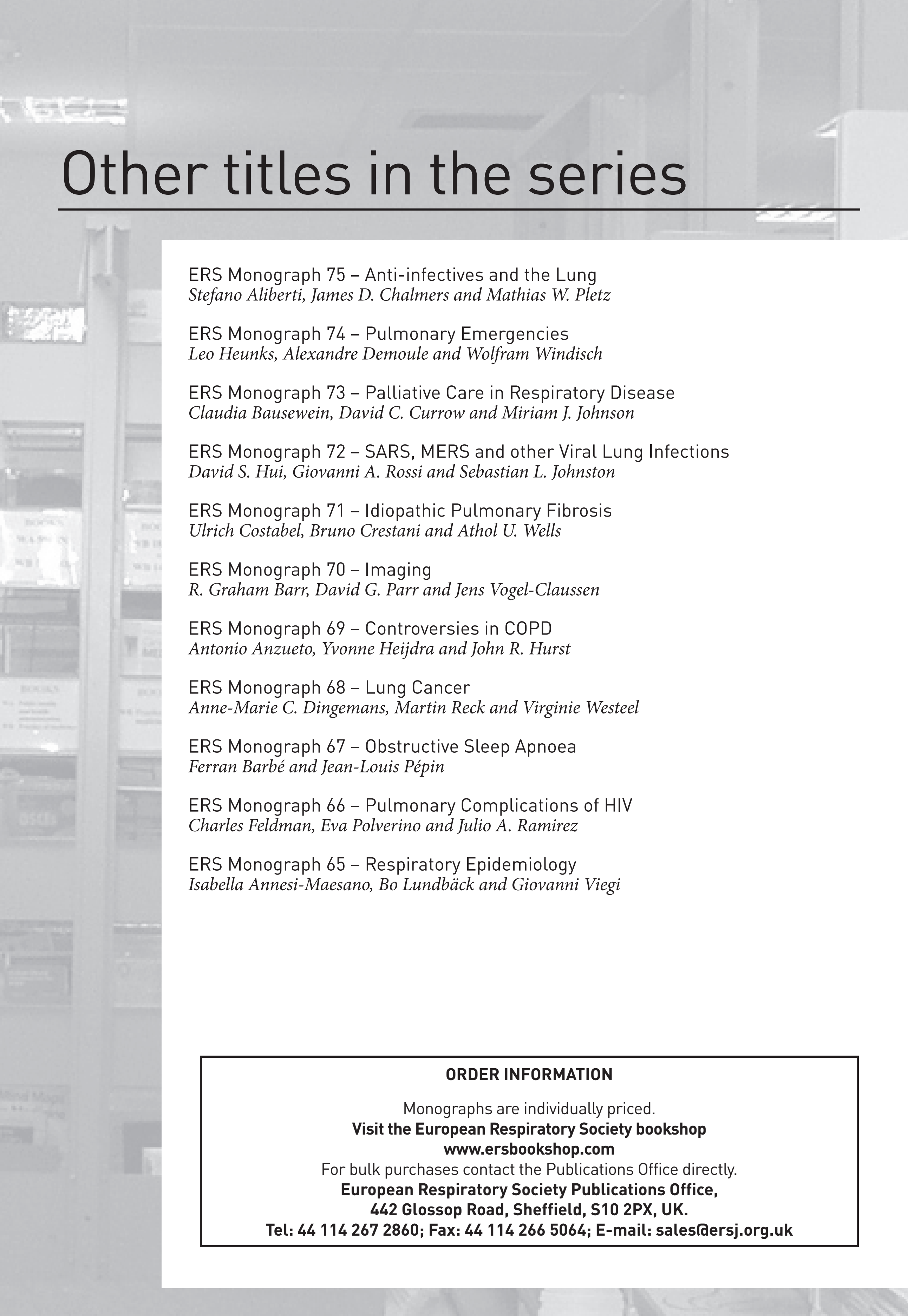

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